Large-scale visuospatial cognition in Williams syndrome and typically developing children

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I, Hannah Jayne Broadbent, confirm that the work presented in this thesis my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Williams syndrome (WS) is a neurodevelopmental disorder of known genetic origin. A characteristically uneven cognitive profile in WS, with a marked contrast between poor small-scale visuospatial ability relative to stronger verbal ability, is well documented. Recent findings demonstrate visuospatial deficits pervade to large-scale navigation abilities in this group. Experimental studies presented in this thesis investigate the nature of large-scale visuospatial impairment in WS at the level of behaviour, as well as the genetic contributions to the WS visuospatial profile. As an important basis on which to understand the nature of atypical development in WS, the thesis also examines the development of large-scale spatial cognition in typically-developing (TD) children. Developmental changes in the use of different spatial frames of reference to mentally represent spatial information both on small-scale tasks and during navigation in large-scale virtual environments were observed in TD children between 6 and 8 years of age, with an adult-like pattern of performance acquired between 8 and 10 years. The findings in TD children provide novel insight into the nature of processes underlying the use of different aspects of spatial knowledge for navigation. In WS, impairments in both egocentric and allocentric spatial reference frames result in severe detriment to spatial processing at both small- and large scales. However, the data suggest that not all aspects of large-scale spatial knowledge are equally impaired in WS, highlighting the multifaceted nature of visuospatial cognition, and extending our understanding of the profile of relative strengths and weaknesses within the visuospatial cognitive domain in this disorder. An examination of the genetic contribution to the WS visuospatial phenotype from two individuals with partial WS genetic deletions further highlights the diverse nature of visuospatial cognition. These findings provide insight both into the dynamic development of visuospatial cognition in typical development, and the atypical visuospatial phenotype in WS.

Dissemination

Peer-reviewed publications

Data from Study 4 have been accepted for publication in Frontiers in Developmental Psychology:

Broadbent, H., Farran, E.K., and Tolmie, (2015). Sequential egocentric navigation and reliance on landmarks in Williams syndrome and typical development. *Frontiers in Psychology, Section Developmental Psychology*.

Data from Study 5 have been published as a journal article in Journal of Neurodevelopmental Disorders:

Broadbent, H., Farran, E.K., Chin, E., Dubois, S., Metcalfe, K., Tassabehji, M., Turnpenny, P., Sansbury, F. & Karmiloff-Smith, A. (2014) Genetic contributions to visuospatial cognition in Williams syndrome: Insights from two contrasting partial deletion patients. *Journal of Neurodevelopmental Disorders,* 6 (1), 18. DOI: 10.1186/1866-1955-6-18

Data from Study 2 have been published as a journal article in Developmental Science:

Broadbent, H.J., Farran, E.K., and Tolmie, A. (2014) Egocentric and allocentric navigation strategies in Williams syndrome and typical development. *Developmental Science.* DOI: 10.1111/desc.12176

Data from Study 1 have been published as a journal article in Developmental Neuropsychology:

Broadbent, H.J., Farran, E.K., and Tolmie, A. (2014). Object-based mental rotation and visual perspective-taking in typical development and Williams syndrome. *Developmental Neuropsychology,* 39 (3), 205-225. DOI: 10.1080/87565641.2013.876027.

Conference proceedings and seminars

Data from Study 4 was presented at the Neurodevelopmental Disorders Seminar Series, 2014, Durham, UK.

Broadbent, H., Farran, E.K., Tolmie, A., (2014) A reliance on visual-matching for navigation in Williams syndrome. Oral presentation.

Data from Study 4 was presented at the European Conference on Psychological Theory and Research on Intellectual and Developmental Disabilities (ECIDD), 2014. Linköping, Sweden:

Broadbent, H., Farran, E.K., Tolmie, A., (2014) Sequential egocentric navigation and reliance on landmarks in Williams syndrome and typical development. Oral presentation.

Data from Studies 2 and 4 were presented at the Institute of Education Postgraduate Research Seminar, 2014:

Broadbent, H.J. (2014) Large-scale spatial coding and spatial navigation strategies in Williams syndrome. Seminar presentation.

Data from Study 2 were presented at the British Psychological Society (BPS) Developmental Section annual conference, 2012. Glasgow, UK:

Broadbent, H.J., Farran, E.K., and Tolmie, A. (2012) Egocentric and allocentric navigation strategies in typical development and Williams syndrome. Oral presentation.

Data from Study 2 were presented at the International Williams Syndrome Association Conference 2012. Boston, MA., USA:

Broadbent, H.J., Farran, E.K., and Tolmie, A. (2012) Egocentric and allocentric navigation strategies in typical development and Williams syndrome. Oral presentation.

Data from Study 2 were presented to the Developmental Neurocognition Lab, Birkbeck, UK:

Broadbent, H.J., Farran, E.K., and Tolmie, A. (2012) Egocentric and allocentric navigation strategies in Williams syndrome. Oral presentation.

Data from Study 2 were presented as a poster at the Neurodevelopmental Disorders Seminar Series, 2012. Kingston, UK:

Broadbent, H.J., Farran, E.K., and Tolmie, A. (2012) Egocentric and allocentric navigation strategies in Williams syndrome. Poster presentation.

Data from Study 1 were presented as a poster at the British Psychological Society (BPS) Developmental Section annual conference, 2011. Newcastle, UK:

Broadbent, H.J., Farran, E.K., and Tolmie, A. (2011) Mental rotation in children and the use of egocentric and allocentric navigation strategies in large-scale space. Poster presentation.

Data from Study 1 were presented to the Developmental Neurocognition Lab, Birkbeck University, UK:

Broadbent, H.J. and Farran, E.K. (2011) Mental rotations of the self and objects in typical development and Williams syndrome. Oral presentation.

Design and Methods from Studies 1 and 2 were presented at the Williams Syndrome Foundation annual convention, 2011.Crawley, UK:

Broadbent, H.J. and Farran, E.K. (2011) Mental rotation and large-scale navigation strategies in Williams syndrome. Oral presentation.

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Chapter 1

Literature review and introduction to thesis

1.1 Introduction

The development of successful navigation skills in humans is imperative to learning how to negotiate our way around novel and diverse environments. Moreover, the need to acquire accurate and efficient large-scale spatial abilities becomes increasingly important throughout development in the pursuit of independent living. This is particularly pertinent to individuals with learning disabilities who are often not afforded the same level of autonomy or opportunities for independence as typical children and adults, especially in relation to travel and navigating around their environments. Williams syndrome (WS) is a relatively rare neurodevelopmental disorder, often resulting in mild to moderate learning disability. Characterised by an uneven cognitive profile, serious impairments on visuospatial tasks in WS are often reported in comparison to relatively proficient performance in other cognitive domains such as language and face processing (Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000) – for a more extensive overview, see 1.5. Research examining visuospatial skills in WS has focussed predominantly on performance on small-scale spatial tasks. However, more recent findings suggest that such difficulties may have possible implications for large-scale navigation in this group (e.g., Nardini, Atkinson, Braddick, & Burgess, 2008). For individuals with WS, impaired navigation abilities may have profound ramifications on their confidence and quality of life, and may contribute to mental health difficulties such as depression and anxiety that are commonly associated with the disorder (Howlin, Elison, Udwin, & Stinton, 2010; Howlin & Udwin, 2006).

The processes by which typically developing (TD) children and adults interact with their surroundings, and are able to encode, store, and recall spatial information for use in any given space has been a matter of some debate within the literature. Of particular interest has been the nature and development of different spatial frames of reference underlying human spatial cognition, the ability to encode spatial relationships between different environmental features, and even whether individuals can form

holistic mental representations or 'cognitive maps' of spatial layouts. An examination of the typical development of these abilities throughout this thesis therefore provides an essential basis on which to understand the nature of atypical development of visuospatial cognition in individuals with WS. For the most part, this thesis examines the nature of large-scale spatial cognition in WS compared to typically developing (TD) children. However, some elements of small-scale spatial knowledge are also assessed in these groups, by way of examining the extent to which performance on tasks at different spatial scales can predict performance at other scales, and to provide discussion regarding the multifaceted nature of human visuospatial cognition.

Differences exist in the processes involved in acquiring spatial information from small- compared to large-scale space (Ittelson, 1973). Spatial knowledge of a large-scale environment requires multiple observations from different vantage points, as the environment and locations within it cannot be observed from one single position. Surveillance of large-scale space therefore necessitates movement and active participation (Kuipers, 1978, 1982). This is contrasted with small-scale spatial knowledge, which refers to an understanding of space that can be experienced in full from a single vantage point, without the need for a change of observer location. Different spatial scales are therefore defined by the different perceptual and motoric processes involved in exploration, and not necessarily by the relative size of space. Researchers have suggested that a number of distinct underlying cognitive processes and neural structures may be involved in learning and performance on spatial tasks of different scales (Allen, Kirasic, Dobson, Long, & Beck, 1996; Freundschuh & Egenhofer, 1997; Hardwick, McIntyre, & Pick, 1976; Siegel, Herman, Allen, & Kirasic, 1979; Tversky, Bauer Morrison, Franklin, & Bryant, 1999; Zacks, Mires, Tversky, & Hazeltine, 2000). Conversely, others have identified a considerable amount of shared variance between small and large-scale spatial learning, suggestive of overlapping processes involved in developing spatial representations across different sized environments (e.g., Hegarty, Montello, Richardson, Ishikawa, & Lovelace, 2006).

In the typical population, notable individual differences exist in spatial navigational abilities, including differences in preferred use of strategies to acquire and use spatial information (Hirtle & Hudson, 1991; D. R. Montello & Pick, 1993; Pazzaglia & De Beni, 2001; Wolbers & Hegarty, 2010). This introductory chapter will discuss the literature examining the development and use of different types of spatial cognitive strategies and spatial frames of reference that underlie different aspects of large-scale spatial knowledge. An additional discussion of the neural correlates of these different aspects of spatial cognition will also be presented. The consideration of large-scale spatial cognition in typical development will allow insight into the factors underlying changes in spatial knowledge throughout ontogeny and the individual differences seen in navigational abilities in typical children and adults.

Examining these areas of the literature will provide an important basis on which to begin to understand the specific nature of large-scale spatial difficulties in WS and the implications of this for the following research. This chapter will also underline the visuospatial cognitive profile associated with WS, highlighting the particular small- and large-scale visuospatial deficits already identified in individuals with this disorder. Prominent theories of spatial cognitive difficulties in WS will be discussed, with reference to known structural and functional abnormalities in WS in cortical regions associated with spatial cognition. The implications of visuospatial difficulties in WS for large-scale navigation will be discussed, providing the basis for the subsequent research hypotheses considered throughout this thesis.

1.2 Typical development of large-scale spatial cognition

1.2.1. Stage theories of large-scale spatial learning

Two prominent theoretical frameworks regarding the development of large-scale spatial knowledge that have been significantly influential in the field of cognitive psychology are those of Piaget and Inhelder (1967) and Siegel and White (1975). Despite critical evaluation, these theories have provided a robust basis on which the majority of research in this area has been set. Piaget and Inhelder (1967) proposed that

during the early stages of a child's conceptualisation of space, a child relies only on their primitive understanding of *topological* relationships between a limited number of objects or landmarks, whilst disregarding metric relations; for instance, having an understanding of the order of a route, but without an understanding of the spacing between objects on the route or length of the route. In the second stage of spatial knowledge development, Piaget described the addition of *projective* understanding, where the child becomes able to infer object relations that are dependent on the individual's viewpoint. Piaget then stated that it is not until a child is older, by 9 to 10 years of age that they are able to grasp *Euclidean* concepts, where object locations are coded metrically. Within this perspective, Piaget claimed that progress should be considered as relative to the maturation of general cognitive abilities and constrained by a child's stage of ontological development (Piaget & Inhelder, 1967).

Based on this Piagetian view, Siegel and White (1975) proposed a hierarchical model in which the development of spatial cognition transitions from 'landmark knowledge' to 'route knowledge' and finally to the development of 'configurational knowledge' or a 'cognitive map' of an environment. Other terms have also been used throughout the literature to denote the mental representation associated with configurational knowledge, including 'survey', 'global', 'relational', 'holistic' 'viewpoint-independent', or 'allocentric' knowledge. Although these terms will be used interchangeably throughout this thesis, 'survey' and 'allocentric' knowledge will be primarily used to refer to the mental representation of an environment and the spatial frame of reference associated with this representation, respectively. For further descriptions of these terms, see *Glossary*.

Within Siegel and White's (1975) framework, 'landmark knowledge' predominantly relates to understanding perceptual information about individual locations, objects, or scenes. 'Route knowledge' on the other hand refers to the knowledge of the temporal, goal-directed and sequential order of landmarks within a given route. In the third stage, mental representations of clusters of landmarks are acquired, leading to an enduring and viewpoint-independent representation in which an

individual develops an understanding of the spatial relationships between places. Here, the spatial relationships learnt are between different environmental locations, irrespective of the navigator's perspective (hence termed 'viewpoint-independent').

As an expansion to Piaget's theory regarding the development of children's spatial knowledge, Siegel and White (1975) proposed that learning occurs both *ontogenetically* as a child develops, and *microgenetically* through repeated experience within an environment. Thus, this framework suggests that children and adults both conform to the same sequence of learning in the development of organised spatial mental representations. Two claims of this theoretical framework therefore suggest that, firstly, young children are not able to develop relational/configurational knowledge of an environment and, secondly, the development of such knowledge in older children and adults may only occur through repeated experience in an environment. These claims have been examined extensively in the literature, with varying results.

In support of this framework, a number of studies have found that very young children do not immediately form survey representations of space (Anooshian & Nelson, 1987; Cousins, Siegel, & Maxwell, 1983; Herman, Shiraki, & Miller, 1985). For example, Cousins et al. (1983) found that whilst children aged between 7 and 11 years were all able to successfully and efficiently navigate through novel routes, only older children were able to infer spatial relations between locations, and therefore succeed on cognitive mapping tasks. Similarly, others have shown that an ability to select landmarks precedes the ability to identify and select route information (Allen, Kirasic, Siegel, & Herman, 1979; Cornell, Heth, & Broda, 1989). In a study of the underlying abilities that facilitate age-related changes in spatial knowledge, Allen and Ondracek (1995) found that landmark knowledge was associated with the development of recognition-in-context memory (the ability to recognise features when presented within their original learning context), and route knowledge was related to the emergence of paired-associative learning (the ability to learn pairs of items so that the presentation of one evokes recall of the other). Thus, in line with a Piagetian-style framework, this

suggests that spatial learning is mediated by the emergence of a number of low-level cognitive abilities across development.

Siegel and White's (1975) theoretical framework asserts that more complex spatial representations can ensue, not only throughout development, but also from increased experience within an environment. This is seen in typical adults, where mental representations of well-travelled layouts are found to be more detailed and integrated than those of less traversed areas (Golledge & Spector, 1978). Indeed, the use of computational modelling has also demonstrated a positive relationship between the amount of experience in an environment and the development of more complex survey representations (Kuipers, Tecuci, & Stankiewicz, 2003). Similarly, configurational knowledge in adults is disrupted following disorientation in a novel environment, but not in an overlearned, familiar environment (Holmes & Sholl, 2005). In contrast to a rigid stage theory however, this study does indicate that, in typical adults, some relational information is coded immediately in a novel environment, albeit vulnerable to disruption following a change of viewpoint.

In developmental studies, both an increased familiarity of an environment and the provision of landmarks have been shown to enhance spatial representations in children as young as 5 years of age (Siegel & Schadler, 1977). Here, children were asked to create models of their classrooms following varied extents of experience (i.e., at the beginning or end of the school year). The authors found that increased experience in an environment facilitated understanding of the positions of individual objects ('absolute accuracy'), but was not sufficient to develop an understanding of the interrelations between objects ('local relational accuracy'). This relational accuracy *was* however found to increase with the provision of landmarks (where a few landmark cues were provided in the model). These effects were found to be independent of maturational factors. Of note however is that this study did not take into account the possibility that children younger than 5 years may already be able to encode spatial-relational information from the environment; particularly as, on small-scale spatial tasks, relational knowledge may be attained by very young children (Bushnell, McKenzie,

Lawrence, & Connell, 1995; Huttenlocher, Newcombe, & Sandberg, 1994; Landau, Gleitman, & Spelke, 1981; Newcombe & Huttenlocher, 2000).

Annoshian and Young (1981) found that some children have advanced spatial knowledge, particularly of their own neighbourhood. This again suggests that experience is an important facilitator of the development of complex spatial mental representations in children. The authors found that children aged 7–14 years had all developed spatial knowledge of the location of landmarks in a familiar environment. However, improvements could be seen with age in the accuracy of pointing to the same landmarks from different locations. This implies that although experience is an important factor, the development of more complex spatial representations is further dependent on age. In a later study, Anooshian and Nelson (1987) examined children's knowledge of directional relationships between different landmarks in their neighbourhood and whether performance was related to the extent of experience navigating in that area. The findings showed that, unlike the findings of Anooshian and Young (1981), children aged 10 and 12 years were poorer at estimating the direction of landmarks from unfamiliar compared to familiar reference points. These findings support the hypothesis that posits children's spatial-relational knowledge begins to develop at about 10 years of age, and requires familiarity of the given space (Siegel & White, 1975). However, even 10 year-olds in this study had good directional knowledge and it may be that this is evident in children below this age. Indeed, when children as young as 5-6 years of age are supported to evaluate and reflect on 'Euclidean' concepts of space, they are able to develop more holistic representations of their environments (Davis & Hyun, 2005). This supports counter-arguments which suggest it is not the case that young children are unable to construct relational concepts of space, but that the ability to integrate and synthesise spatial information undergoes a more protracted course of development (Clements & Battista, 1992).

Even though familiarity in an environment has been shown to play a key role in the development of detailed spatial knowledge in school-aged children, there is also empirical support for even earlier development of spatial relational knowledge in 3-4

year olds (Conning & Byrne, 1984). This study examined the idea that cognitive map knowledge of an environment may actually occur, firstly as topological 'network maps' that are void of distance knowledge or relative bearings, and secondly, as 'vector maps', which are representations of the environment that involve encoding of distance and direction information. Conning and Byrne (1984) examined preschool children's ability to point to out-of-sight locations in familiar and novel contexts. If children were found to point to locations using a 'crow-flight' method, this was taken to indicate the presence of 'vector map' knowledge, opposed to pointing towards the path down which one would need to travel to reach the location, indicative of only 'network map' understanding. The results showed that in a novel environment, children were unlikely to show vector knowledge. However, in a familiar context such as the home, many 3 and 4 year-olds showed evidence of accurate vector knowledge, which could be considered as similar to Piagetian Euclidean awareness or relational knowledge. Thus, it was concluded that in young children, the type of spatial knowledge expressed is situation dependent, unlike that proposed by a relatively inflexible stage theory.

Instead of the ability to gradually develop survey knowledge of an environment, Pick (1972) proposed that young children's understanding of a spatial layout is comprised of a number of small representations that are poorly integrated. In one study, Kosslyn, Pick, and Fariello (1974) found that, when asked to judge distances between objects located in a space that was subdivided into quadrants by 2 transparent and 2 opaque barriers, adults perceived locations separated by opaque barriers as further apart. Children, on the other hand, overestimated distance judgements between both types of barriers, suggesting that their representations of the individual quadrants were poorly integrated into a holistic cognitive map. The authors concluded from this, in support of a Piagetian viewpoint, that children are influenced by the concept of functional distance (judgements concerning the length of time it would take to traverse from A to B, for example) to a greater extent than adults, who would be more likely to take into account the metric properties of different layouts. However, in replicating this study, Newcombe and Liben (1982) found that children showed no developmental difference in the way in which they estimated distances, including between opaque and transparent

barriers. Newcombe and Liben (1982) concluded that the problems children show on Kosslyn's original task may be due to difficulties in rank ordering (when asked to rank in order the closeness of objects) and not distance judgements. This was seen as children had a greater tendency than adults to group their rankings by quadrant.

It is evident therefore that spatial abilities of young children do develop and become more fine-tuned with age, but also with increased familiarity in an environment. For example, when children between 5 and 13 years of age were asked to point to landmarks within their school, a difference in accuracy was found that was dependent on age, gender, and experience, but with the largest difference seen in 10-11 year-olds outperforming 7 year-olds (Lehnung, Leplow, Haaland, Mehdorn, & Ferstl, 2003). The specific spatial skills expressed in young children may be dependent on the type of space and the procedures used to measure and elicit spatial knowledge. In particular, the size of space may play an important role in the type of spatial representation elicited. When asked to navigate through four to six rooms and determine which object would be in an adjacent room, children aged 3-5 years were unable to make spatial inferences (Hazen, Lockman, & Pick, 1978); however, in a later study when the size of space was reduced and children were given fewer cognitive demands, children as young as 3 years were able to infer spatial relationships accurately (Hazen, 1982). The authors concluded from this that young children's ability to understand spatial relationships and develop a basic survey representation of an environment is dependent on both the size of space and the cognitive load required for the task. Similarly, Herman, Shiraki and Miller (1985) found that in a very large environment, 5 year-olds were more able to point to imperceptible locations than 3 year-olds even when information-processing demands were significantly reduced and the environment was familiar to all children.

1.2.2 Beyond stage theories

Even within typical development, refinement of spatial knowledge seems complex and is dependent on multiple factors. Theoretical frameworks that propose a stage-like process of learning are typically generalised to adults. It is considered that by

adulthood, individuals would have developed the ability to utilise each type of spatial navigation knowledge; however, it is proposed that in novel environments, a similar trajectory of knowledge acquisition will occur, with each stage learned individually and in order. Despite the influential nature of Siegel and White's (1975) stage theory, little consensus is found within the literature as to the acquisition of spatial knowledge in adults. Indeed, recent research in typical adults has cast doubt on the transitional nature of spatial knowledge.

In adults, the type of spatial mental representation that develops from experience in an environment may to some extent rely on the nature of the spatial information that is encoded during the learning phase. In line with this, adults who receive spatial information from consistently switching perspectives (route or survey perspectives), are able to develop 'perspective-free', viewpoint-independent mental representations, demonstrating an ability to understand the interrelationships between places in an environment from all viewpoints, regardless of whether that viewpoint has been previously experienced (Lee & Tversky, 2005). In two experiments, Taylor, Naylor, and Chechile (1999) asked adult participants to learn information about either an environmental layout (survey goal) or the fastest route through the environment (route goal). Within these groups, participants were either asked to learn from a map or by navigating a route (two learning conditions). Results indicated that both the spatial goal and learning condition (why and how information is learned) influence the representation of the spatial perspective that develops and spatial knowledge outcome. For instance, map-learners performed more accurately than route-learners on survey-knowledge tasks, whereas route-learners presented with superior route-perspective knowledge. When the spatial goal was to learn the environmental layout (survey goal), this also positively influenced performance on the relative spatial knowledge task, regardless of the learning condition. In a later study, Brunyé and Taylor (2008) found that when adult participants are only given 'route' descriptions to learn a spatial layout, extensive experience is needed in order to develop a more global mental representation, or 'cognitive map' of the environment. Conversely, such extensive experience and time was not required for participants who learnt the spatial layout using more spatial-

relational descriptions. This indicates that developing a holistic mental model of space from a route description is more time consuming than when learning from a survey description. This may be due to survey descriptions of environments being more likened to map-like learning, which contains important viewpoint-independent details. Importantly, results of this study also showed that after only one session of learning route descriptions, adults were able to make inferences about the spatial layout and relationships within the environment, albeit not to the level of those in the survey-description condition. This is a phenomenon that would not be predicted by stage theories of spatial learning that propose a gradual transition from route to survey knowledge. The authors surmised that learning from route descriptions only requires the use of a basic egocentric spatial frame of reference (understanding the location of environmental features in relation to the self), which is thought to be required for landmark and route knowledge. In contrast, they suggest a more complex allocentric frame of reference (understanding the interrelationships between environmental features), which is required for survey knowledge, is used during learning of an environment through global or map-type descriptions. It should be noted that this research was conducted with adult participants. Given that children are able to use an egocentric frame of reference earlier in development than an allocentric one (Nardini, Burgess, Breckenridge, & Atkinson, 2006; Nardini, Thomas, Knowland, Braddick, & Atkinson, 2009; Piaget & Inhelder, 1967), this may have important implications for the use of these different spatial representations and understanding of large-scale space throughout development. The development of these different spatial frames of reference will be discussed later in more detail (see 1.2.3).

From research with adults it has been argued that original frameworks, which propose a sequential learning trajectory of navigational knowledge (e.g., Siegel & White, 1975), do not provide an explanation for the mechanisms by which one develops from one stage to the next (D. R. Montello, 1998). For instance, while familiarity in an environment does clearly play an important role in gaining more robust spatial representations, it may not independently facilitate the development of a global spatial-relational understanding as stage theories would suggest (D. R. Montello, Hegarty,

Richardson, & Waller, 2004). Montello (1998) argued that, in typical adults, configurational knowledge of distance and direction may be ascertained very early in the learning of a novel environment. This implies that no stage exists in which adults solely encode and store landmark knowledge or topographical relations. Montello (1998) also argued that, with increasing familiarity in an environment, there is a quantitative and continuous increase in spatial knowledge, in contrast to the proposed qualitative transitional shift. Moar and Carleton (1982) similarly argued that in adults an initial understanding, or schemata, of individual routes may not be necessary for survey knowledge. The authors found that during the early stages of navigation in a novel environment, adults were able to form integrated cognitive maps (survey knowledge) using information from intersecting networks of routes and not just through learning single routes independently. This supports the proposition that the development of survey knowledge may be less stage-like than suggested by Siegel and White, with individual routes not necessarily learned in isolation, but simultaneously.

In a longitudinal study, Ishikawa and Montello (2006) examined how spatial knowledge of an environment develops over time in adults. The findings showed that even though landmark and route knowledge were both gained after the first exposure to the environment, participants also exhibited some degree of metric knowledge during the early stages of learning. The study also highlighted large individual differences in the pattern of learning, with individuals who showed good performance in the first sessions continuing to be good throughout the trial, and poorer early performers remaining poor throughout, with no significant improvement from beginning to end. These findings imply that instead of a 'progression' from one stage to the next occurring in a fixed order and driven by familiarity, the accuracy of configurational knowledge may principally be down to individual differences. Others have similarly argued that navigational performance is influenced by individual differences in information processing and variability in brain microstructure (Wolbers & Hegarty, 2010). Consequently, if individual differences are the key to the extent of learning then it may be that poor navigators can be trained to develop more complex survey knowledge.

It is worth noting here that in contrast to the majority of the aforementioned research, others have even argued that there is little convincing evidence that adults are able to develop global 'cognitive maps' that contain integrated metric information about distances, angles and the interrelationships within a given environment (e.g., Foo, Warren, Duchon, & Tarr, 2005; Moeser, 1988). In four experiments, Foo and colleagues (2005) examined the process by which adults could determine novel shortcuts in medium-sized environments. The results showed that even though participants were able to learn two paths of a triangular route, their ability to then determine the novel shortcut down the third path was variable. When landmarks were stable, and therefore reliable, adults were able to make use of these to perform more accurate shortcuts. However, in conditions where landmarks were not available, and participants should supposedly rely on metrically-based survey knowledge, shortcuts taken were often erroneous. Importantly, the findings did show that in the absence or unreliability of landmarks, a more basic form of relational knowledge could be used and, alongside landmark knowledge, is acquired early on in the learning phase. Therefore, the relational knowledge that did develop was argued to be rudimentary and lacking Euclidean information. Foo et al. (2005) found that by covertly moving the location of landmarks, participants incorrectly continued to use these to find a novel shortcut. However, it should be noted that the nature of the experiment may have led participants to believe that they should follow the landmarks. In addition, some participants noticed the landmark shift, suggesting that these individuals must have had a certain amount of accurate metric and relational knowledge in order to determine this change, even if the metric information could not be used to accurately guide navigation.

In light of such behavioural studies, and alongside results of neuroimaging research, a more recent attempt to develop a framework of understanding spatial navigation aims to take into consideration the connection between brain and behaviour (Chrastil, 2013). In particular, Chrastil has proposed an extension to the current framework to include a further form of spatial knowledge; graph knowledge, which is positioned between route and survey knowledge. Here, graph knowledge is reported to incorporate the sequential information and place-action associations of a route, with

some information about how locations are connected, but does not necessitate the path integration (metric knowledge) of survey representations. Within this new taxonomy, the four types of spatial knowledge are therefore seen to include seven distinct and yet often over-lapping cognitive processes, some of which also include a number of sub-processes; displayed in 1.2.2.1 Table 1.

The proposed taxonomy by Chrastil (2013) advocates for the fluidity of spatial knowledge via the over-lapping nature of the processes and sub-processes. The author acknowledges that even with the development of this extended framework, there exists little consensus as to the neural correlates of each level of spatial knowledge. Indeed, although some mapping exists between preferential activation in certain brain regions and each aspect of spatial cognition, it is likely that multiple brain regions are involved in each process, dependent on factors such as (but not limited to) the nature of the task demands, what is attended to in the environment, and individual variability. Furthermore, the main categories of spatial knowledge that are distinguishable at the behavioural level are not necessarily always found to have distinct neural correlates (although see, Shelton & Gabrieli, 2002; Wolbers & Buchel, 2005; Wolbers, Weiller, & Büchel, 2004). Instead, Chrastil (2013) proposes that neural correlates of the cognitive processes and sub-processes are more easily identifiable and distinct. This will be taken into account throughout this thesis in discussions regarding brain-behaviour correlations of spatial cognition. The neural basis of large-scale spatial cognition is discussed further in 1.4.

1.2.2.1 Table 1. A taxonomy of spatial knowledge (from Chrastil, 2013)

	Landmark	Route	Graph	Survey
1	Place recognition *Scenes and views*	Place recognition *Scenes and views*	Place recognition *Scenes and views* *Place within larger environment*	Place recognition *Scenes and views* *Place within larger environment*
2		Sequence learning	Sequence learning	
3	Identifying decision points	Identifying decision points	Identifying decision points	
4		Response learning		
5		Forming associations	Forming associations	
6			Locating the goal *Relate goal and current location* *Transformation between ego- and allocentric perspectives*	Locating the goal *Relate goal and current location* *Transformation between ego- and allocentric perspectives*
7				Path integration

The four categories of spatial knowledge are divided into seven cognitive processes, some of which are further divided into sub-processes (*italics*).

To conclude, the studies discussed above suggest that the acquisition of spatial navigational knowledge in typical adults, should not be thought of as clearly defined stages. Indeed, neither should all individuals be considered able to employ clear way-finding strategies in all navigational situations. It may even be that, for some individuals, spatial relational knowledge remains imprecise and incomplete (Gärling & Golledge, 2000), particularly in poor navigators. These studies however only provide insight into the process by which *adults* learn to navigate novel environments and do not offer an explanation for spatial learning across development. In the literature, some parallels have been proposed between the ontogenetic development of large-scale

spatial knowledge in children and the microgenetic development of such knowledge in a novel environment in adults. However, differences lie in the nature of influences that drive each type of development, and little can be reasoned about stage changes in children based on adult performance. That said, the developmental literature discussed earlier similarly suggests that the learning of landmark, route and survey knowledge may not always progress in a static order. Although behavioural frameworks may be useful for understanding the different classifications of large-scale spatial knowledge in children, there may be a number of factors (both maturational and environmental) that influence the acquisition of navigational knowledge.

1.2.3 Development of spatial frames of reference

The research discussed above has for the most part focussed on typical adults and the neural underpinnings of different aspects of large-scale spatial cognition. With regards to the underlying processes involved in the use of different aspects of spatial navigational knowledge, recent research has examined the different spatial frames of reference used for mentally representing spatial information. An examination of changes with development in the ability to use different spatial frames of reference may provide an important basis on which to understand the processes that underlie the ability to use different aspects of large-scale spatial knowledge from landmark to survey knowledge with age.

Spatial frames of reference refer to the particular relational systems or 'orientation frames' used to define the relative positions of objects and/or the self in space (Kuipers, 1978). In the literature, predominantly two main terms are used to classify types of spatial reference frames or strategies used for goal-orientated navigation, namely 'egocentric' (also sometimes called idiothetic) and 'allocentric' (sometimes termed allothetic) reference frames (Klatzky, 1998; Maguire et al., 1998). An egocentric frame of reference refers to the understanding of locations in space with respect to the particular perspective of the navigator, and involves the use of body-centred coordinates. In relation to categories of spatial navigation, route knowledge is

concomitant with the use of an egocentric frame of reference, given the need to understand the location of the self in relation to specific viewpoints and landmarks when making decisions throughout a route. Conversely, an allocentric frame of reference relates to a framework that is external to the perceiver and independent of his or her own position. This usually refers to the knowledge of the spatial relationships between independent objects or elements within an environment. Survey knowledge would therefore be considered allocentric, and 'viewpoint-independent', given the need to understand the location of landmarks relative to other environmental locations, regardless of whether they had been previously viewed by the navigator from any given location.

Research into animal spatial navigation and orientation has been used to gain insight into human navigation and the use of different spatial frames of reference. Non-human species such as ants (Collett & Collett, 2000; Müller & Wehner, 1988) and bees (Dyer, Berry, & Richard, 1993) have been found to predominantly use path integration systems, which allow for complex navigational capabilities. During the process of path integration, an animal moves through its environment, maintaining a continuously updated egocentric representation of their location relative to the position of a chosen object or their home that is used as a vector point (Müller & Wehner, 1988). This also enables the specification of distance and direction information.

Wang and Spelke (2002), proposed that representations underlying the majority of human spatial behaviour are "momentary, egocentric, and limited" (R. F. Wang & Spelke, 2002 pg. 376). The authors suggest that humans use egocentric 'place recognition' and 'path integration' strategies, and an allocentric 'geometric module' for re-orientation that uses environmental surface structure information but does not hold information about the spatial properties of landmarks. Here, place recognition is considered a viewpoint-dependent strategy by which an individual is thought to recognise landmarks and scenes by matching their current view to a 'snap-shot' representation stored in memory. This is in line with the cognitive process proposed by Chrastil (2013), underlying all aspects of spatial knowledge. In contrast with Wang and

Spelke's model however, in humans the use of path integration in large-scale space has been found to be minimal, possibly due to the increased difficulty in continually estimating one's position as the size of space increases (Waller, Loomis, & Steck, 2003). That said, grid cells and heading-direction cells in the human entorhinal cortex are thought to support the encoding of metric information associated with the process of path integration (Doeller, Barry, & Burgess, 2010; Jacobs, Kahana, Ekstrom, Mollison, & Fried, 2010; Taube, 1998).

More recently and in contrast with Wang and Spelke, Burgess (2006) proposed a 'two-system' model in which egocentric and allocentric representations exist in parallel and may cooperate with each other in some situations when employed simultaneously. This is observable in typical adults, who are able to acquire egocentric and allocentric representations simultaneously when navigating in a new environment and can subsequently apply the use of each spatial frame of reference spontaneously when required (Iglói, Zaoui, Berthoz, & Rondi-Reig, 2009). Similarly, Mou and colleagues (2004) have advocated for the existence of two subsystems within human spatial cognition; an egocentric and an environmental subsystem, similar to the often-named allocentric processing system. This model suggests that adults are able to form enduring representations of inter-object spatial relationships, by employment of an environmental subsystem, that can be used to keep track of their location and to locate objects around them (Mou et al., 2004). As such, perceptual-level egocentric representations (the egocentric subsystem) would only be put into use when the individual is oriented in line with an array and when spatial representations within the environmental (or allocentric) subsystem are inaccurately formed or indiscriminate. This is supported by evidence from adults when learning the layout of a novel environment (Mou, McNamara, Rump, & Xiao, 2006). Results of a further study by Mou and colleagues (2008) indicate that scene recognition may be 'intrinsic-orientation-dependent' and not exclusively 'viewpoint-dependent' as advocated by Wang and Spelke (2002). This was shown in a group of adults, as recognition of a scene was easier when two out of three objects were presented on the intrinsic-direction line (a mental representation of the layout of objects from an alternative orientation to the

participant's viewing position) than when two out of three were presented along the participant's original viewpoint line during the learning phase.

It is now well understood, therefore, that in typical adults different spatial reference frames may function in parallel (Iglói et al., 2009; Nadel & Hardt, 2004). Although there remains some debate regarding the specific nature of spatial frames of reference used by adults during navigation, the superseding conclusion from the majority of leading models is that adults have the ability to develop both a basic body-centred mental representation of space that is dependent on one's viewpoint, and that of a more complex mental representation that integrates the interrelationships within a particular environment. The existence of these different processes have been supported not only through experimental tasks, but also by functional brain imaging techniques, which have identified associations between activity in different brain regions during tasks that elicit the use of these different spatial frames of reference, and will be discussed further in 1.4.

Research into whether children and adults perform similarly on such spatial tasks however, is minimal. Understanding the specific way in which the use of spatial frames of reference develop throughout infancy and early childhood may have important implications for determining the processes by which children interpret and solve both small- and large-scale spatial tasks.

As discussed in 1.2.1, according to the views of Piaget & Inhelder (1967), in early cognitive development children are bound by body-centred egocentric coding systems, with a later shift to external, allocentric reference systems. This shift with age has been supported in a number of developmental studies (e.g. Acredolo, 1978). However, this matter has been contentious within the literature and a number of authors have argued that different spatial frames of reference may undergo more complex developmental trajectories (e.g. Nardini et al., 2006). In contrast to the idea of a later developmental shift to the use of allocentric representations, during small-scale tasks, infants as young as 4 months old have been shown to use external, object-centred frames of reference to code the location of an object (Bremner, Bryant, & Mareschal,

2006). Between the ages of 12-16 months, infants become even more able to integrate metric information in their spatial coding (Acredolo, Adams, & Goodwyn, 1984; Newcombe, Huttenlocher, Drummey, & Wiley, 1998). This may be indicative of a developmental increase in the ability to apply more appropriate spatial frames of reference to encode spatial information in different tasks.

On small-scale tasks, children have been found to be flexible in their coding of spatial locations from a young age (Newcombe & Huttenlocher, 2000; Uttal, Sandstrom, & Newcombe, 2006), with children as young as 4 years able to use knowledge of either the relationship between two landmarks as the basis for spatial coding when locating a hidden object, or distance and direction information between an object and a single landmark. In addition, by 4-5 years of age, children show signs of being able to switch from an egocentric to an allocentric frame of reference when required, demonstrated by their ability to use the order of landmarks in a model to determine the location of hidden objects (Kannass, Plumert, McDermott, Moore, & Durich, 2004). Therefore, instead of a decisive shift from simple egocentric to more complex allocentric representations through early development, it may be that the nature of spatial coding changes, with allocentric coding being more successfully and appropriately applied to guide navigation with increasing age. Thus, with development, children may acquire even greater flexibility in applying the appropriate spatial-coding strategy (Uttal et al., 2006).

Nardini and colleagues (2006; 2009) have provided important insight into the development of spatial frames of reference. Using an array of cups on a moveable board that were surrounded by toys with fixed locations for use as potential landmarks, Nardini et al. (2006) tested children aged 3-6 years on their ability to recall the location of an object placed under one of the cups in a number of different rotation conditions. Spatial frames of reference that were available to support performance were manipulated on the basis of either a rotation of the array, or a movement of the participant to a new viewpoint (including control conditions of a rotation of 'both' or 'neither'). Findings showed that children between 3 and 6 years were able to use an egocentric representation to solve the 'neither-move' (neither the array nor the

participant moves) and 'both-move' conditions. The use of a room or environmental frame of reference was also evident by 3 years of age, with an advantage for 'child-move' over 'array-move' conditions, thus suggesting that children at this young age are not as purely egocentric as originally proposed by Piaget (Piaget & Inhelder, 1967). When both body- and room-based frames of reference were available, this resulted in an additive effect meaning that they were able to utilise the information from both. However, the ability to recall locations when only the array was moved (viewpoint-independent), and thus requiring the use of spatial relations intrinsic to the array, showed a more protracted course of development, with this ability not emerging until 5 years of age.

This later emergence of 'viewpoint-independent' processing in spatial memory has been supported further (Nardini et al., 2009). Here however, 5 year olds were only able to employ viewpoint-independent recall when details about self-movement or indirect visual cues were presented. This provides support for the hypothesis that there may be a developmental change from a reliance on the use of viewpoint-dependent to viewpoint-independent representations, with greater flexibility in the use of the latter between the ages of 6 and 8 years. The study showed that a process for recalling the location of a hidden object that will be based on the structural information of the layout develops later than a process that uses view-matching and self-motion.

Despite these findings on small-scale tasks, little is understood about the use and significance of different frames of reference during navigation in large-scale space (McNamara, Rump, & Werner, 2003), and certainly throughout development. In response to this, Bullens and colleagues (Bullens, Iglói, Berthoz, Postma, & Rondi-Reig, 2010) examined the ontogenetic development of the spontaneous use of sequential egocentric and allocentric strategies during navigation. Using a virtual StarMaze task, the authors showed that, for the most part, children between 5 and 10 years spontaneously employed a sequential egocentric strategy, rather than an allocentric strategy, during the task when allowed to use a spontaneous strategy. However, in a task where the use of an allocentric strategy was imposed, even the younger children

were able to perform well on the task. Additionally, children showed a progressive use of a spontaneous allocentric strategy across the age range, with performance comparable to adults (Iglói et al., 2009) by 10 years of age. This supports a differential pattern of spontaneous use of egocentric and allocentric strategies between the ages of 5 and 10 years, with the ability to develop complex representations of an environment to guide navigation occurring from 10 years of age.

1.3 The relationship between small- and large-scale spatial abilities

1.3.1 Small-scale mental rotation and large-scale navigation in adults

It is clear from the literature that there may be differences in the use of environmental features such as landmarks and spatial frames of reference both across development and between individuals. However, the nature of the cognitive processes that underlie individual differences in navigational and way-finding abilities is not well understood. A number of studies have shown that some adult navigators prefer to use global, allocentric representations of space, whereas others continue to use landmark-based strategies even in highly familiar environments (Pazzaglia & De Beni, 2001), and without significant detriment to way-finding (Passini, 1984). Indeed, while some adult navigators rely on the use of response strategies to recall a known route, others prefer to use complex spatial-relational strategies that afford the use of novel short-cuts (Marchette, Bakker, & Shelton, 2011). Moreover, others report the ability to flexibly shift between these strategies (Wolbers & Hegarty, 2010).

Researchers have sought to understand whether these different preferences are related to differences in underlying spatial processing. For example, studies in typical adults have identified a relationship between the type of spatial information that is encoded and performance on other spatial tasks such as the ability to mentally rotate geometric shapes, or to imagine one's self moving through an environment (Palermo, Iaria, & Guariglia, 2008; Pazzaglia & De Beni, 2001, 2006; Shelton & Gabrieli, 2004). In one study, Palermo and colleagues (2008) examined the relationship between mental rotation skills and how rapidly participants were able to develop a cognitive map of an

environment, and also how well they were able to use this representation in subsequent way-finding trials. Findings showed that the ability to quickly develop an understanding of the spatial relationships between landmarks was positively correlated with the ability to perform simple mental rotations. However, mental rotation abilities were not related to the ability to use an already developed cognitive map for the purpose of subsequent orientation.

Other studies have shown that adults with poor mental rotation skills prefer to adopt a representation of space based on landmark or route information, whereas individuals with superior mental rotation abilities have a preference for more global relational representations (Pazzaglia & De Beni, 2001, 2006). In a study examining gender differences in navigation, mental rotation skills were found to be significantly correlated with way-finding but were not as necessary for way-finding in females as they were for males (Malinowski, 2001). Malinowski and colleagues concluded that this may be due to a greater reliance on landmarks in females, whereas males tend to use more global, configurational strategies that would require mental rotation skills; a finding previously posited by Dabbs, Chang, Strong, and Milun (1998).

Differential patterns of neural activity have been identified for route and configurational learning (Shelton & Gabrieli, 2002) and also for retrieval following route and configurational encoding (Mellet et al., 2000). Shelton and Gabrieli (2004) examined the extent to which individual differences in mental rotation skills are related to the ability to form representations of survey or route information at the neural level. Their findings showed that mental rotation ability positively correlated with decreased activation during survey encoding in anterior cingulate, frontal, and parietal regions, but not with activation changes during route encoding. This suggests that the processes associated with activation in these regions may be used more efficiently for survey learning in individuals with superior mental rotation ability. As such, individuals with poorer mental rotation abilities may rely on additional or alternative and more inefficient processing for both route and survey encoding. These findings provide interesting insight into how differential brain activation as a function of small-scale

spatial skills such as mental rotation may be associated with diverse information processing strategies.

1.3.2 Small-scale spatial abilities and navigation in typical development

In developmental research, it has remained a matter of debate whether small-scale spatial abilities, such as mental rotation, correspond to or even predict abilities required for spatial navigation and orientation in large-scale space (Allen et al., 1996; Hegarty & Waller, 2005; Quaiser-Pohl, Lehmann, & Eid, 2004). Notably, Quaiser-Pohl et al. (2004) examined the relationship between the ability to form large-scale spatial representations and small-scale spatial abilities in children aged 7-12 years. By comparing standardized tests of spatial abilities such as Piaget's 'Water-Level task' and the 'Mental Rotations test' with environmental navigation abilities and cognitive mapping skills, the authors did not find any substantial correlations. This suggests that large-scale spatial knowledge may be independent from small-scale spatial abilities in children, indicating that a distinction should be made between these constructs. For this reason, it may be inaccurate to assume that children who present with poor small-scale spatial skills would also be impaired in large-scale way-finding tasks, and vice-versa. However, this study did not examine the changes that may occur with age in the relationship between small and large-scale spatial skills. It could be that an increased ability to use alternative spatial frames of reference with development and more mature navigational strategies may correspond more to small-scale spatial abilities.

Although other research has also found no relationship between small and large-scale spatial abilities, even in adults (Hegarty & Waller, 2005), this may be a reflection of the measures used in these studies and the specific spatial constructs examined in both the small- and large-scale tasks. Using alternative measures, other authors *have* identified relationships between small- and large-scale spatial abilities (Bryant, 1982; Fenner, Heathcote, & Jerrams-Smith, 2000; Purser et al., 2012)

Fenner et al. (2000) studied age-related changes in the cognitive underpinnings of way-finding behaviours; examining whether environmental knowledge was related to

visuospatial abilities (as measured by mental-rotation, visualisation, Corsi block, and paper-folding tasks) and verbal abilities (including verbal reasoning, comprehension, and knowledge), and whether this relationship was constant across development. Findings showed that children with high levels of visuospatial abilities performed better on way-finding tasks than children with poorer visuospatial skills. However, this was only found for younger children aged 5-6 years, and not for children aged 9-10 years. In contrast, no effect of verbal ability in either age group was identified, indicating that verbal processing may not be imperative to successful way-finding. Therefore, although visuospatial abilities may be important for way-finding at 5-6 years of age, there may be differences in the underlying cognitive processes that are important for spatial navigation abilities at different developmental time-points.

Underlying cognitive processes associated with large-scale spatial abilities may therefore be diverse and shift according to task demands. The following section discusses two types of mental transformation abilities that have been shown to relate to different aspects of large-scale spatial knowledge. An examination of these different abilities will provide a basis on which to understand the different processes that may be related to diverse aspects of navigational ability both in adults and across development.

1.3.3 Two types of small-scale mental transformation

In the renowned work by Piaget and Inhelder (Piaget & Inhelder, 1967, 1971), a distinction was theorised between a child's ability to mentally rotate an object or array to an alternative imagined position, and the ability to determine the perspective of an array of objects from an alternative imagined viewpoint. A number of other authors have similarly identified a dissociation between object-based (or array-centred) and body-based (or 'visual perspective-taking') mental transformations (Hegarty & Waller, 2004; Huttenlocher & Presson, 1973; Simons & Wang, 1998; Wraga, Creem, & Proffitt, 1999; Zacks et al., 2000).

These two types of imagined rotation differ in the coordinate spatial frames of reference that are mentally manipulated in order to obtain the final imagined perspective.

In object-based (OB) mental rotation, the imagined position of an object or array can be mentally rotated relative to either an environment- (centred on relationships between features within an environment) or an OB frame of reference (centred on the relationship between features within the rotating object), whilst one's body-based (egocentric) frame of reference remains stable. OB mental rotations therefore require the use of an allocentric spatial representation (an understanding of the constancy of the spatial relationships within in the array or object to be rotated). This allows an individual to imagine what an object would look like at alternative orientations, without the need for actual or imagined self-movement. In contrast, during visual perspective-taking (VPT) tasks, an individual imagines their own body-based (egocentric) rotation or movement within or around an array or environment relative to a fixed allocentric frame of reference. VPT transformations therefore involve spatial updating of the location of the self within a fixed environment. This allows an individual to imagine what a scene would look like from an alternative viewpoint.

Although performance on these two types of mental transformation are highly correlated (Hegarty & Waller, 2004), a measurable distinction between OB mental rotation and VPT is supported by neuroimaging data. That is to say, in adults, OB and VPT tasks are associated with increased activity in two discrete yet overlapping neural systems (Zacks et al., 2000; Zacks, Ollinger, Sheridan, & Tversky, 2002; Zacks, Rypma, Gabrieli, Tversky, & Glover, 1999). This suggests that these aspects of spatial cognition are dissociable both at the behavioural and neural level. Research examining the neural bases of these abilities and the changing nature of OB mental rotation and VPT throughout development will be discussed in more detail in study 1 (see chapter 2).

1.3.4 Object-based rotation, visual perspective-taking, and navigation

Research into the relationship between mental transformation and navigational abilities has focused for the most part on OB mental rotation (Hegarty & Waller, 2005; Palermo et al., 2008). However, little acknowledgement has been given to the role of VPT abilities as a function of large-scale spatial knowledge (Kozhevnikov, Motes,

Rasch, & Blajenkova, 2006). Defining the differences between these types of mental transformation abilities in the way that they relate to different aspects of navigation may help to highlight the multifaceted nature of large-scale spatial cognition.

With a measurable distinction between OB and VPT rotation evident in the literature, Kozhevnikov and colleagues (2006) sought to examine this further in relation to large-scale navigation abilities. In this study, the authors compared performance in typical adults on a number of navigational tasks, including retracing routes, finding short-cuts, pointing to occluded locations, and drawing the route on a map, with small-scale perspective-taking, array-rotation, and object-rotation tasks. The results showed that, in typical adults, VPT ability uniquely predicted navigational task performance, which required participants to accurately encode the spatial relationships between objects with respect to their own body-based frame of reference. For example, VPT was particularly related to the ability to determine a short-cut and the ability to update one's location following a detour. Perspective-taking ability was also correlated with the ability to accurately point to hidden locations from different places within a familiar environment.

It is not clear from this whether this would be a robust pattern across development. Children have difficulties in spontaneously applying an allocentric strategy in navigation until about 5-7 years of age (Bullens, Iglói, et al., 2010). It may be that this is related to a difficulty in the use of viewpoint-independent representations needed for mental transformation tasks at this age. Therefore, children who have difficulties in VPT may also show poorer performance on tasks that entail determining novel short-cuts and pointing tasks that indicate the development of spatial-relational understanding. This will be examined in chapter 4.

1.4 Neural correlates of large-scale spatial knowledge

An examination of the neural foundations of large-scale spatial knowledge provides an important basis on which to examine the development of different spatial cognitive processes and sub-processes (Chrastil, 2013) in both TD children and individuals with WS. Research including neuroimaging, single-cell recordings and

lesion studies has identified a network of brain regions that subserve spatial information processing, including the hippocampus, parahippocampal region, entorhinal and retrosplenial cortices, the posterior cingulate, and precuneus (Burgess, 2008).

Successful performance on large-scale spatial navigation tasks may therefore be dependent on the integrity of cortical structures such as the medial temporal lobe, which undergo a protracted course of development throughout childhood (Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Gogtay et al., 2006). Indeed, Overman, Pate, Moore, and Peuster (1996) argued that as spatial relational tasks are not performed accurately until the age of 7, this suggests that the medial temporal lobe and related cognitive abilities may not have developed fully until this point.

From animal research, the discovery of place cells in the hippocampus (O'Keefe & Nadel, 1978), grid cells in the medial entorhinal cortex (Hafting, Fyhn, Molden, Moser, & Moser, 2005), and head direction cells in structures within the limbic network known as the Papez circuit (Taube, 1998) indicate the existence of an intrinsic neural network involved in allocentric navigation and the formation of survey representations of large-scale space (Jeffery & Burgess, 2006). Specifically, studies of spatial processing in rats (R. G. M. Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978) and humans (Maguire, Burgess, & O'Keefe, 1999; Pigott & Milner, 1993) have identified the hippocampus as playing a key role in large-scale navigation, and particularly allocentric processing (Burgess, Maguire, & O'Keefe, 2002; O'Keefe & Nadel, 1978). In contrast to this, Eichenbaum and colleagues (Eichenbaum, 2000; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999) argued that the hippocampus may just be involved in general relational processing and not solely involved in spatial information. However, neuroimaging data has shown that in adults, hippocampal activation is only driven by *spatial* relational processing and not by relational processing demands in other domains (Kumaran & Maguire, 2005). This provides support for the role of the hippocampus in the development of survey representations of large-scale space in humans.

Specific developmental differences in the formation of the hippocampus have been identified. For instance, a reduction in the volume of the anterior hippocampus can be seen between the ages of 4 and 25 years, whilst the volume of the posterior hippocampus increases throughout this period (Gogtay et al., 2006). This may have important implications across childhood for the development of spatial processing abilities that depend on these different hippocampal regions. For instance, during the formation of survey knowledge, the anterior hippocampus plays a crucial role, whereas the posterior hippocampus is implicated in the retrieval and employment of these survey representations to be able to navigate within an environment (Iaria, Chen, Guariglia, Ptito, & Petrides, 2007). Thus, later maturation of the posterior hippocampal cortex may be related to developmental differences in the ability to retrieve survey-type representations for use during navigation. Iaria and colleagues (2007) also found that during the retrieval of a previously formed 'cognitive map', brain areas that were preferentially activated included the retrosplenial cortex, bilateral parahippocampal cortex and right posterior hippocampus, equally. These cortical regions likewise undergo a protracted course of development (Ghetti et al., 2010). Further to this, findings from a neuroimaging study with TD adolescents and adults suggests that the maturation of allocentric spatial coding is in line with age-related functional changes to a left-lateralised neural network that subserves verbal abilities (Pine et al., 2002). This indicates that the development of other cognitive skills including language may also serve to facilitate the use of more complex spatial representations. As mentioned earlier, Fenner et al. (2000) found that verbal ability was not related to navigational abilities in children below 10 years. However, neuroimaging findings hint that this may not be the case for later in development.

The parahippocampal region and retrosplenial cortex (located in cingulate cortex) have been shown to be distinct and yet complimentary in human navigation, and provide important inputs into neighbouring hippocampal and entorhinal cortices (Epstein, 2008). In a review of the literature, Epstein (2008) argued that the parahippocampus is involved in the learning of the topographical information of a novel environment and the encoding of spatial information in a viewpoint-dependent frame of

reference. Indeed, during navigation in a virtual maze where all landmarks and intersections were designed to look identical from any approach and so participants had to rely solely on egocentric representations, the parahippocampal cortex was preferentially activated (Weniger et al., 2010). Weniger and colleagues (2010) also concluded that the parahippocampal cortex may be involved in the translation between egocentric and allocentric spatial memory in the construction of stable survey representations.

As discussed in 1.2.3, adult spatial navigation is flexible and dynamic, with the capacity to switch between allocentric and egocentric representations depending on the task at hand (Iglói et al., 2009). This ability to switch between using different spatial frames of reference may occur gradually throughout childhood in relation to the maturation of the hippocampus and associated areas. The retrosplenial cortex has also been identified as having a role in updating an individual's location and viewpoint used, by translating between the spatial frames of reference employed during a task (Byrne, Becker, & Burgess, 2007; Iaria et al., 2007). For example, this area manages inputs from both egocentric and allocentric reference frames (Maguire, 2001), transforming information from an egocentric frame of reference supported by the parietal cortex, caudate and parahippocampal regions (Weniger, Ruhleder, Wolf, Lange, & Irle, 2009; Weniger et al., 2010), to an allocentric reference frame supported by the hippocampus (Burgess, Maguire, Spiers, & O'Keefe, 2001). Chrastil (2013) argues that this transformation between egocentric and allocentric representations relates to an understanding of how certain locations fit within the context of the larger environment (i.e., knowledge of relative directions and distances of other locations), a cognitive sub-process characteristic of both graph and survey knowledge (see 1.2.2.1 Table 1).

The development of graph and survey representations of an environment when learning a new route from an egocentric perspective may therefore rely on the transformation of egocentric spatial information, into the use of an allocentric reference frame, dependent on these cortical regions. Using a virtual-reality paradigm, Wolbers and Buchel (2005) found a distinct dissociation between the hippocampus and

retrosplenial cortex but with both areas suggested to be involved in reorientation. The results showed that activity in the hippocampus was related to the amount of spatial relational information acquired, regardless of whether this occurred in an early or later stage of learning. The retrosplenial cortex however, was employed throughout the learning phase, integrating egocentric spatial information and self-motion cues increasingly across learning sessions. This parallels behavioural measures of increased survey knowledge with experience in an environment.

The use of either an egocentric or allocentric strategy for navigation in a large-scale environment is therefore supported by different patterns of cortical activation. Furthermore, using fMRI, Jordan et al. (2004) found preferential activation of the medial temporal areas, parahippocampus, hippocampus, and thalamus in individuals who used an allocentric strategy during navigation in a virtual environment, but not those using an egocentric strategy. The authors concluded that this is implicative of a memory and attention processing network that is specifically involved in the encoding and retrieval of spatial-relational knowledge such as involved in graph and survey representations.

Neuroimaging studies with adults have also given light to the neural processes involved in the encoding of spatial information and use of specific environmental information during navigation and way-finding. In particular, research into the neural correlates of landmark use has provided important insight into large-scale spatial processing. Such findings parallel behavioural data that suggests landmarks at decision points facilitate navigation along newly learned routes (Jansen-Osmann, 2002; Janzen & Weststeijn, 2007). Using a virtual environment route-learning paradigm, fMRI results have shown preferential cortical activation in the parahippocampal place area (posterior parahippocampal gyrus) for landmarks at decision points compared to those at non-decision points (Janzen & Weststeijn, 2007). In addition, in a real-world experiment, this increased activation at decision-points was only found for areas of a route that were unfamiliar to participants prior to the study (Schinazi & Epstein, 2010). Also, increased activation in the retrosplenial cortex during the processing of direction information was

found at these decision points; activation that was similarly more prominent along newly learned sections of a route (Schinazi & Epstein, 2010). This cortical network may therefore be particularly involved in spatial learning in novel environments.

The above findings indicate that, certainly in typical adults, neural correlates of route knowledge are dependent on factors such as familiarity of the environment. Indeed, successful adult navigators show preferential activation of the anterior right hippocampus when determining a novel route between known landmarks, but the head of the right caudate is preferentially activated when following a well-learned route (Hartley, Maguire, Spiers, & Burgess, 2003). This is in agreement with findings of different neural representations for response learning and place learning in rats (Tolman, Ritchie, & Kalish, 1946). The study by Hartley et al. (2003) also showed that whilst following a well-learned route, navigators activate a neural network that is separate from medial temporal lobe structures, supported instead by the parietal cortex and caudate. This indicates that once a route is well rehearsed, an action-based representation of the environment is typically used, reducing the cognitive load. This is seemingly in contrast with a stage-like process of navigational learning (Siegel & White, 1975), which emphasises that egocentric associative-based learning occurs before route and survey learning. This instead demonstrated that the acquisition of some aspects of spatial knowledge may occur at similar time-points during learning.

As mentioned previously, in a review of the neuroimaging studies into human spatial navigation, Chrastil (2013) suggests that the neural correlates of spatial memory do not neatly align with each main category of landmark, route, graph or survey knowledge. Instead, the data suggest that more distinct mappings may exist between neural activity and the underlying cognitive processes and sub-processes involved (as outlined in Chrastil's 2013 taxonomy presented in 1.2.2.1 Table 1). In summary, the author underlines that in typical adults, the learning of scenes and views (a cognitive process that is involved in each main category of spatial knowledge) is supported by the parahippocampal place area (e.g., Maguire, Frackowiak, & Frith, 1997). However, when a navigator places landmarks within the context of the larger environment, as seen

in graph and survey knowledge, this is likely supported by retrosplenial (e.g., Epstein & Higgins, 2007) and hippocampal (e.g., Burwell, Saddoris, Bucci, & Wiig, 2004; Doeller, King, & Burgess, 2008) activity. The hippocampus is further implicated in spatial sequential learning (e.g., Maguire et al., 1997), which is an element of both route and graph knowledge. Furthermore, parietal brain regions and the caudate are associated with habitual response-learning (Hartley et al., 2003) and egocentric spatial representations (Galati et al., 2000; Shelton & Gabrieli, 2002, 2004). Allocentric and metric representations for survey knowledge on the other hand involve entorhinal (Spiers & Maguire, 2007) and hippocampal (Morgan, Macevoy, Aguirre, & Epstein, 2011) regions. As such, each category of spatial knowledge that can be defined distinctively at the behavioural level is likely to involve a number of different brain regions, depending on the task at hand. Likewise, individual cortical regions may be involved in multiple aspects of spatial knowledge. These findings have important implications for research examining the acquisition of large-scale spatial knowledge both in TD children and individuals with WS. In particular, behavioural measures of large-scale navigational abilities should take into account the possible neural correlates of learning, consolidation and retrieval, with respect to the dynamic process of typical brain development and the possible cascading effects of atypical cortical maturation.

1.5 Williams syndrome

1.5.1 WS genotype and phenotype

Williams syndrome (WS) is a relatively rare autosomal dominant disorder arising from a submicroscopic deletion on the long arm of chromosome 7, at locus 7q11.23 (Frangiskakis et al., 1996; Osborne, 2012); a hemizygotic deletion involving approximately 27-28 genes (Koehler, Pabst, Pober, & Kozel, 2014; Schubert, 2009). This typically results in a deletion spanning some 1.55 to 1.84 megabases of genomic DNA (Antonell et al., 2010; Bayés, Magano, Rivera, Flores, & Pérez Jurado, 2003; Pober, 2010; Schubert, 2009; Tassabehji et al., 1999) (see 6.1 for further details). Differing prevalence rates of WS have been reported, although it is understood to be

estimated as occurring between one in every 7,500 (Strømme, Bjømstad, & Ramstad, 2002) and 20,000 (C. A. Morris & Mervis, 1999) live births. WS is sometimes also referred to as Williams-Beuren syndrome; however, the term WS will be used hereafter throughout this thesis.

The distinctive WS phenotype typically comprises vascular stenosis, connective-tissue abnormalities, and a characteristic craniofacial dysmorphology that includes a flattening of the nasal bridge, broadening of the nose and anteverted nostrils, long philtrum, wide mouth with full lips, small jaw, and a prominent supraorbital ridge (Donnai & Karmiloff-Smith, 2000; Ferrero et al., 2007; C.A. Morris, 2011; C.A. Morris, Demsey, Leonard, Dilts, & Blackburn, 1988). Individuals with WS are also often reported to experience hyperacusis (over-sensitivity to certain frequencies), and phonophobia (fear of loud or sudden noises) (Gothelf, Farber, Raveh, Apter, & Attias, 2006; Johnson, Comeau, & Clarke, 2001). Infantile hypercalcemia, related to significantly high levels of blood calcium, is also common in WS (Kruse, Pankau, Gosch, & Wohlfahrt, 1992). Other medical complications include abnormalities of the musculoskeletal, renal and endocrine systems (C.A. Morris et al., 1988), dental problems (malocclusion), and joint impediments (Kaplan, Kirschner, Watters, & Costa, 1989). These characteristics are indicative that WS is a progressive and multi-system disorder. In addition to the physiological characteristics, at the behavioural level, individuals with WS present with a hypersociable disposition (Arnold, Yule, & Martin, 1985), social and emotional atypicalities (Davies, Udwin, & Howlin, 1998) and mild to moderate learning disability (Howlin et al., 2010).

Diagnosis of WS is based on phenotypical information and confirmed by genetic testing. Early identification of WS can initially follow the detection of cardiac abnormalities (predominantly in the form of supravalvar aortic stenosis [SVAS], in around 75% of cases (Bruno, Rossi, Thüer, Córdoba, & Alday, 2003)), or of the atypical WS facial physiognomy (Preus, 1984). Genetic diagnosis is then confirmed by a fluorescence *in-situ* hybridization (FISH) test for the deletion of the elastin gene (*ELN*) from the middle of the WS critical region at 7q11.23 (Curran et al., 1993; Ewart, Jin,

Atkinson, Morris, & Keating, 1994). *ELN* has been found to play a critical role in the regulation of arterial morphogenesis (Li et al., 1998) and the deletion of one *ELN* allele can be detected in 96 percent of patients presenting with WS (Lowery et al., 1995). Other DNA-based diagnostic techniques are also available, such as array-comparative genomic hybridisation, although the FISH test is most commonly used.

WS is associated with a distinctively uneven cognitive, behavioural and neuroanatomical profile, characterised by relative strengths and weaknesses within and across different cognitive domains (Bellugi et al., 2000; Bellugi, Wang, & Jernigan, 1994; Martens, Wilson, & Reutens, 2008). Individuals with this disorder therefore provide important insight into human cognition. In relation to the uneven profile, WS is typically associated with profound impairments in visuospatial, numerical and planning abilities contrasting with relatively good verbal abilities, face processing skills, and elevated levels of sociability (e.g. J. Atkinson et al., 2001; Bellugi et al., 2000; Bellugi et al., 1994). Even within a single cognitive domain seemingly divergent abilities can appear. For instance, impairments that have been identified in auditory long-term memory are seen to occur alongside relative good auditory short-term memory abilities (Vicari, Brizzolara, Carlesimo, Pezzini, & Volterra, 1996).

Most commonly reported in WS is a dissociation between verbal and non-verbal abilities, with poor visuospatial cognition occurring alongside relatively proficient linguistic processing (Arnold et al., 1985; Bellugi et al., 1994; Rossen, Bihrle, Klima, Bellugi, & Jones, 1996). However, it is important to note that linguistic abilities in WS are not 'intact', but emerge only as a *relative* strength (Karmiloff-Smith, Brown, Grice, & Paterson, 2003; Karmiloff-Smith et al., 1997). Indeed, children with WS often present with a neuropsychological profile of strengths and weaknesses even within the language domain, with stark contrasts found between aspects of comprehension and production (Pezzini, Vicari, Volterra, Milani, & Ossella, 1999). It has been suggested that the often-cited distinction between verbal and spatial abilities may be due to a non-linear development of different cognitive functions in WS, with verbal abilities developing at a faster rate than non-verbal abilities (Jarrold, Baddeley, & Hewes, 1998).

This would therefore result in a more distinct contrast between these abilities with increasing maturation. Furthermore, language abilities in WS may be considered atypical due to development occurring under differential constraints to that in typically developing individuals (Thomas et al., 2001). In their study, Thomas and colleagues found that children with WS showed a greater reliance on phonological representations and relatively poor use of semantics in early development, which is likely to result in an atypical developmental trajectory.

Given the known genetic origin in WS, research into the disorder has provided important insight into genotype-phenotype interactions and the nature of gene expression. This is particularly so in relation to the way in which certain genes are expressed in the brain. Recent research developments using animal knockout models and the examination of individuals with atypical or partial deletions within the WS critical region have provided some insight into the contribution of individual genes from the 7q11.23 locus to the complex WS phenotypic profile (e.g. X. Meng et al., 1998; Osborne, 2010). Currently however, only the *ELN* gene has been linked explicitly with a particular phenotypic expression in WS, namely the presence of SVAS (Osborne, 2012; Pober, 2010). Other clear one-to-one genetic and phenotypic correlations remain elusive. That said, hemizygosity (where only one of a gene pair is present) for genes at the telomeric end of the WS critical region such as *GTF2IRD1* and *GTF2I,* and *CLIP2*, may greatly contribute to the presentation of a number of the characteristic WS features (Vandeweyer, Van der Aa, Reyniers, & Kooy, 2012). For instance, *GTF2IRD1* has been proposed to play a significant role in the syndrome-specific craniofacial features (Tassabehji et al., 2005), and *GTF2I* in the associated intellectual disability in WS (C.A. Morris et al., 2003). Given also that these general transcription factors (GTFs) regulate the expression of other genes, their deletion is likely to be particularly significant in phenotypic expression across development.

An in-depth phenotyping of the visuospatial domain in individuals with differing partial WS genetic deletions may provide further insight into the genotypic relations to the WS visuospatial cognitive profile. The contribution of differential gene expression

to the visuospatial cognitive phenotype in WS is discussed further in study 5 (see chapter 6).

1.5.2 Small-scale visuospatial cognition in WS

Difficulties in WS on small-scale (table-top) visuospatial tasks are well documented in the literature (e.g., Bellugi, Sabo, & Vaid, 1988; Hoffman, Landau, & Pagani, 2003). Largely, visuospatial impairments have been demonstrated with the use of standardised construction tasks such as the Block Design (e.g., Wechsler Intelligence Scale for Children; Wechsler, 1949) or Pattern Construction (Differential Ability Scales; Elliott, 1990), which require an individual to reconstruct two-dimensional designs using three-dimensional blocks with solid-coloured or two-coloured (diagonally or vertically divided) surfaces. These are used as proxies for everyday visuospatial construction involved in undertakings such as tying shoe laces, laying a table, or assembling flat-pack furniture. Individuals with WS are found to perform at or below the bottom of the typical range on such tasks (Mervis, Robinson, & Pani, 1999), in line with TD 4 year-olds (J. Atkinson et al., 2001).

A number of explanations as to the possible cognitive processes or aberrant functions underlying poor visuospatial construction performance have been put forward. Findings suggest that these difficulties do not result solely from early sensory visual impairments such as strabismus or poor visual acuity (J. Atkinson et al., 2001), or from motor difficulties (Bellugi et al., 2000), although these are commonly reported in WS. Early explanations of visuospatial impairments pointed to a preference in WS to process 'local' elements at the expense of processing 'global' information (Bellugi et al., 1994). However, more recent research has consistently indicated that local and global perceptual processing in WS are similarly impaired (Deruelle, Rondan, Mancini, & Livet, 2006; Farran & Jarrold, 2003; Hoffman et al., 2003; Pani, Mervis, & Robinson, 1999). Moreover, differential processing biases in WS have been shown to arise from the type of processing demands of the task, with a local processing bias evident in

drawing tasks, but with no bias of processing in perceptual and identification tasks (Farran, Jarrold, & Gathercole, 2003).

The pattern of visuospatial deficits in WS has been partly attributed to impairments identified in dorsal stream structure and function; the dorsal stream deficit hypothesis (J. Atkinson et al., 2001; J. Atkinson et al., 2003; J. Atkinson et al., 1997). In typical adults the dorsal cortical visual system is involved in processing and encoding the spatial location of objects and visually guided actions (Felleman & Van Essen, 1991), in contrast to the ventral visual stream that supports perceptual object recognition (Goodale & Milner, 1992). Although this cortical vulnerability is not unique to WS, poor performance on measures of dorsal stream functioning in comparison to relatively good performance on ventral stream measures has provided important insight into the possible underlying neural basis of such contrasting difficulties in WS (J. Atkinson et al., 1997).

Findings from neuroanatomical research such as reduced volumes of grey matter in an area of the superior temporal lobe in WS (Eckert et al., 2005) and reduced sulcal depth in parietal regions (Kippenhan et al., 2005) further advocates a dorsal stream dysfunction in WS. In addition, abnormalities of the intraparietal sulcus have been implicated (Meyer-Lindenberg et al., 2004); although, these findings suggest that this may only lead to a selective impairment in dorsal stream functions, resulting in a lesser impact on other dorsal stream processes (Meyer-Lindenberg et al., 2004; Meyer-Lindenberg, Mervis, & Berman, 2006). Similarly on behavioural tasks, Stinton, Farran, and Courbois (2008) found that atypical dorsal stream processing is fractionated in WS, with some processes less affected than others. As stated above, a dorsal-stream dysfunction is not specific to WS and has been implicated in other disorders (J. Atkinson & Braddick, 2011; Braddick, Atkinson, & Wattam-Bell, 2003). As such, the dorsal stream deficit hypothesis may not wholly explain the idiosyncratic pattern of visuospatial impairments in this disorder. A more detailed examination of the specific cognitive difficulties typically expressed in WS, and how this relates to known underlying deficits in cortical functioning is therefore required.

Difficulties in mental imagery have been implicated as one factor underlying poor performance on visuospatial tasks in WS (Farran, Jarrold, & Gathercole, 2001). Using the Children's Embedded Figures Test and a Squares Task, Farran and colleagues found that individuals with WS processed local and global perceptual information in a manner comparable to that of typically developing (TD) individuals. A difference between the groups, however, was shown on a mental rotation task, with the WS group demonstrating significantly poorer mental image transformation abilities than the TD group. Farran and Jarrold (2004) concluded that such difficulties may be related to a deficit in the perceptual processing of orientation. Their findings indicated that individuals with WS do not necessarily have difficulties with all types of image transformation, as performance on a transformation of size task - which does not include the demands of orientation - was found to be comparable to that of a non-verbal mental age-matched TD group.

In support of Farran and colleagues, Vicari, Bellucci, and Carlesimo (2006) found that, although no difference was evident between individuals with WS and TD controls on tasks requiring the mental visualisation of objects, the WS group scored significantly below the TD group on tasks that required spatial manipulation and rotation of the images. Moreover, in contrast to performance in TD children (Courbois, 2000; Courbois, Oross, & Clerc, 2007), such difficulties in mental rotation in WS were not found to be remediated through the addition of a salient component in the stimuli (Stinton et al., 2008). Thus, even when stimuli include conspicuous cues such as including one section larger than another, this may not lead to greater accuracy in individuals in WS, suggestive of divergent spatial processing abilities in this group. Of note however, it may be that a dorsal stream impairment in WS contributes to mental rotation difficulties, given the relationship between dorsal steam functioning and mental transformation in typical adults (Podzebenko, Egan, & Watson, 2002).

Research examining atypical processing that may underlie some of the spatial difficulties in WS has more recently examined the use of spatial reference systems on small-scale tasks. For example, Nardini and colleagues (2008) examined the

development of spatial frames of reference in WS on a spatial array task used previously with TD children (Nardini et al., 2006). It was found that children with WS showed delayed development of spatial coding compared to controls. Similar to TD children, older individuals with WS (aged 26-42 years) showed the additive effect of using both body- and environment-based frames of reference when both were available. However, the results highlighted that individuals with WS had more difficulties in using local landmarks in array-based representations (when asked to relocate a hidden object following a rotation of the array), an ability that occurs by 5 years of age in TD children (Nardini et al., 2006). The authors suggested that a difficulty in using the intrinsic relationships between landmarks appropriately may account at least in part for the spatial deficits associated with WS. Such difficulties in the use of landmarks and spatial frames of reference in WS on small-scale tasks may also provide relevant insight into the difficulties in large-scale navigation and the development of functional mental representations of spatial layouts in WS.

1.5.3 Large-scale visuospatial cognition in WS

Despite the profusion of research that has enhanced our understanding of small-scale visuospatial difficulties in WS, there is a relative scarcity of research into large-scale spatial abilities in this group. Difficulties in small-scale spatial cognition in WS are considered to extend to particular problems in spatial navigation based on parental reports of problems with way-finding (J. Atkinson et al., 2001; Farran, Blades, Boucher, & Tranter, 2010). Given the specific difficulties on table-top spatial tasks, it is conceivable that individuals with WS would also display difficulties on large-scale tasks, particularly those requiring the use of similar spatial strategies and frames of reference as used in small-scale tasks such as mental rotation tasks. Indeed, as mentioned above, mental transformation abilities and the use of different spatial frames of reference on small-scale tasks are related to large-scale spatial navigation and way-finding abilities in TD children (Fenner et al., 2000) and adults (Kozhevnikov et al., 2006).

Real-world route learning studies have been used to examine some aspects of large-scale spatial cognition in WS. In one study, Farran et al. (2010) compared individuals with WS to a group with moderate learning difficulties (MLD) and TD children. The data showed that although the WS and MLD groups were able to learn a sequence of landmarks in a novel environment and accurately retrace their route, they had difficulties developing a survey representation of space, which requires an understanding of the environmental spatial relationships. It is not clear, however, whether difficulties in spatial knowledge were due to poor cognitive abilities alone, or whether individuals with WS display syndrome-specific deficits on some large-scale navigation tasks. Moreover, it is uncertain whether the lack of survey knowledge in these groups was due, at least in part, to the limited experience within the environment. This may be important given that in typical development, environmental familiarity can facilitate learning of spatial relationships and the subsequent development of survey knowledge (Anooshian & Nelson, 1987). In a more recent comparison of a WS group and TD children aged 6-9 years in a virtual environment, Farran, Courbois, Van Herwegen, and Blades (2012) found that individuals with WS made significantly more errors learning a route than TD children. On a test of landmark recall following learning, the WS group showed a similar differentiation between junction and path landmarks as TD children (with superior recall of junction landmarks), but this was positively related to the level of nonverbal ability. This is indicative of an atypical developmental pathway in WS.

As suggested above, large-scale spatial difficulties in WS may be related to impaired mental transformation abilities (Stinton et al., 2008) and difficulties in developing a viewpoint-independent representation of space (Nardini et al., 2008). Whilst the ability to use an egocentric representation of space would allow accurate route learning to occur, this would not lead to the development of a viewpoint-independent, survey representation of one's environment, which requires allocentric spatial coding.

Neuroimaging studies with individuals with WS have consistently identified atypical structure and functioning of the parietal lobe regions (Eckert et al., 2005; Kippenhan et al., 2005; Meyer-Lindenberg et al., 2004). Abnormal structure and functioning of the hippocampal formation has also been found in WS (Meyer-Lindenberg et al., 2005). Given the role of these regions in the use of egocentric (e.g., Shelton & Gabrieli, 2002, 2004) and allocentric mental representations (e.g., Iglói, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010; Morgan et al., 2011), respectively, it can be inferred that individuals with this disorder would have difficulties on tasks that require the use of these spatial frames of reference and depend on the integrity of these regions.

The abovementioned behavioural studies alongside neuroimaging data provide insight into the specific large-scale visuospatial difficulties that may arise in individuals with WS. A main strand of enquiry in this thesis will therefore be to further examine the specific difficulties in large-scale spatial processing in this group, particularly the extent to which navigational abilities are related to different mental transformation skills and the use of different spatial frames of reference.

1.6 The use of virtual environments to examine spatial navigation

Research into large-scale spatial abilities has previously relied on the examination of navigation in real-world environments. However, more recently the use of virtual environments (VEs) have provided a positive alternative, allowing for controlled manipulation of an environment and permitting the navigator to traverse layouts multiple times, without fatigue or real-world distractions (Richardson, Montello, & Hegarty, 1999). This is particularly important given the known physical difficulties associated with WS, such as cardiovascular disease and joint limitations. Similarly, elevated levels of anxiety in WS (Dykens, 2003) may impede real-world navigation (Hund & Minarik, 2006), a difficulty that could be alleviated somewhat in VEs that serve to eliminate environmental hazards and reduce unsolicited sounds and distractions.

When navigating through a VE compared to a real one, behavioural performance is largely equivalent (Mellet et al., 2010), and similar cognitive mechanisms underlie

learning to orientate (Richardson et al., 1999). Others have found that survey knowledge acquired from VE navigation is comparable to that acquired in the real world (Regian & Yadrick, 1994; Ruddle, Payne, & Jones, 1997). However, despite showing substantial shared neural activation, some differences are seen in neural activity for VE versus real-world learning (Mellet et al., 2010). This has been attributed to the cortical activity associated with finger and hand movements required to navigate VEs (Mellet et al., 2010).

Some limitations of VEs however include that of a restricted field of vision, such that peripheral information is mostly imperceptible. This is particularly so for desktop VEs compared to more immersive head-mounted VE displays. Moreover, VE navigation does not allow for the acquisition of head-direction or proprioceptive information, which provide important feedback during the development of survey knowledge and path integration in particular (Ekstrom, 2010; Maguire et al., 1999). VEs also only support the use of the visual modality, making it difficult to account for multisensory interactions during navigation (Péruch & Gaunet, 1998). Despite this, studies in typical development and individuals with physical disabilities show that information learnt from VEs can transfer successfully to real-world comparisons (Bailey & Witmer, 1994; Farrell et al., 2003; Foreman, Stanton, Wilson, & Duffy, 2003; Rose et al., 2000; Wallet, Sauzéon, Rodrigues, & NKaoua, 2009; Wilson, Foreman, & Tlauka, 1996). For instance, individuals who have learned routes (Waller, Montello, Richardson, & Hegarty, 2002) or spatial relationships (Richardson et al., 1999) in a VE are not only able to apply the learnt knowledge in the VE itself, but more successfully follow equivalent routes and identify spatial relationships in the real-world. The examination of whether strategies from training environmental learning in WS using VEs is transferable to real-world scenarios is beyond the scope of this thesis. However, this demonstrates that VEs can be taken as suitable equivalents to real-world tasks for the studies presented here, and provide a unique opportunity to study spatial abilities in WS following extended experience in an environment.

1.7 Conclusions and thesis directions

In typical development, the acquisition of spatial knowledge in large-scale space has been a matter of debate for decades. Research with typical adults has demonstrated that the formation of a mental representation of space that includes knowledge of landmarks, routes and spatial-relational properties may not result from a stage-like process as hypothesised by hierarchical theorists (Piaget & Inhelder, 1967; Siegel & White, 1975). The findings from developmental studies however, have been conflicting and have often depended on the type of measures used and spatial processes examined. TD children may be more able to develop spatial relational knowledge earlier than the stage theories suggest, however research has indicated an important role of familiarity in an environment, the size of space and the changing role of landmarks for facilitating navigation throughout development.

In typical adults, a positive relationship has been shown between mental rotation and navigation abilities, especially in the use of survey representations of an environment (Palermo et al., 2008; Pazzaglia & De Beni, 2001). Later development of mental rotation abilities in typically developing children (Childs & Polich, 1979; Marmor, 1975; Piaget & Inhelder, 1971) and the ability to appropriately apply a viewpoint-independent representation of one's environment (Nardini et al., 2006; Nardini et al., 2009) may, therefore, be related to the changes in navigational abilities and particularly spatial-relational knowledge seen across childhood. Similarly, difficulties in individuals with WS on mental rotation tasks (e.g., Vicari et al., 2006) and in the use of viewpoint-independent processing (Nardini et al., 2008) may contribute to the reported difficulties in navigation and the subsequent development of spatial-relational knowledge in this group.

At the cortical level, the ability to form holistic survey representations of one's environment may rely on the integrity of the hippocampus and surrounding brain regions that are known to subserve spatial cognition and navigation (Burgess, 2008; Burgess et al., 2002). Thus, the protracted maturation of these cortical areas in typical development may initiate an improved ability to spontaneously apply appropriate spatial

frames of reference in later childhood. As such, in individuals with WS, atypical development of the hippocampal formation (Meyer-Lindenberg et al., 2005) and of the dorsal stream pathway (J. Atkinson et al., 1997) may contribute greatly to the specific large-scale spatial difficulties evident in this group. Although neuroplasticity in neurodevelopmental disorders should of course be considered, this underlines the possible neural correlates and low-level cognitive processes that are involved in the development of and difficulties in large-scale spatial cognition both in typically developing children and individuals with WS.

The aim of this thesis is to further examine large-scale spatial learning in WS compared to TD children. Within each experimental chapter, specific research questions and hypotheses will be presented for the corresponding study, the findings of which will be drawn together in the concluding chapter. The ability to understand spatial relationships within an environment (necessary for proficient navigational abilities to develop), and the use of different spatial frames of reference in these groups will provide insight into the nature of large-scale spatial cognition in both typical and atypical development. The use of both egocentric and allocentric spatial frames of reference in WS and how these are related to different aspects of spatial cognition will therefore be a main emphasis of this thesis. An analysis of low-level cognitive abilities in WS such as mental transformation of the self and objects, and the relationship with performance on these tasks with large-scale navigational abilities may provide important insight into the specific spatial impairments in this group. In addition to these studies, an examination of the candidate genes on the WS critical region of chromosome 7 that are associated with different aspects of visuospatial ability in WS will be presented. This will offer an insight into the relationships between the WS genotype and visuospatial cognitive phenotype, and also provide a more thorough examination of the nature of large-scale visuospatial abilities both in typical and atypical development.

Chapter 2

Study 1: Small-scale mental rotation and visual perspective-taking in typical development and Williams syndrome

2.1 Introduction

Impaired large-scale visuospatial functioning in WS is often appraised as being an extension of small-scale spatial difficulties. However, the extent to which variance in performance on small-scale tasks predicts large-scale spatial abilities is ambiguous. Moreover, little is known regarding whether tasks at different spatial scales share common underlying processes or neural correlates, particularly in individuals with atypical neurodevelopmental trajectories, and given the multifaceted nature of visuospatial cognition. Indeed, even across typical development little is understood regarding the associations between different visuospatial functions. In typical adults, the most robust associations between small and large-scale measures are between tasks that require imagined transformations of the position of objects or the self (e.g., Hegarty & Waller, 2005; Kozhevnikov et al., 2006). As a precursor to examining large-scale spatial difficulties in WS, therefore, the study presented in this chapter aimed to explore small-scale mental transformation abilities in individuals with WS and typically developing children between 5 and 10 years of age.

2.1.1 Object-based (OB) vs. visual perspective-taking (VPT) abilities

In the field of visuospatial cognition, a distinction can be made between performance on small-scale tasks that require object-based (OB) mental rotation and those requiring body-based (egocentric) visual perspective-taking (VPT) transformations (Hegarty & Waller, 2004; Zacks et al., 2000) (see 1.3.3).

Assessments of OB mental rotation abilities typically requires participants to make same-different judgments between two images that are either identical or mirror-images, one of which is rotated to different orientations (Shepard & Metzler, 1971). Results have shown that in adults, there is a linear increase in reaction time with

increased angular discrepancy between the two images (Shepard & Cooper, 1982; Shepard & Metzler, 1971; Zacks et al., 2000; Zacks et al., 2002). Thus, individuals take increasingly more time to mentally rotate images the further they are misaligned from an upright position in both clockwise and anti-clockwise directions. In contrast, when adults are asked to perform imagined VPT transformations, this finding of a linear increase in response time with greater orientation is no longer observed (Amorim & Stucchi, 1997; Parsons, 1987; Wraga, Creem, & Proffitt, 2000; Zacks et al., 2000). This indicates that adults may use a different cognitive strategy during VPT tasks to that employed in OB mental rotation, leading to better performance on these tasks. It has been argued that this enhanced performance on VPT tasks in adults may be due to the ability to perform 'blink transformations' to immediately update ones location rather than through continuous transformation of the egocentric reference frame (Wraga et al., 2000). However, this is not seen to be the case for degrees of angular disparity greater than about 90° (Kessler & Thomson, 2010; Zacks & Michelon, 2005). Others have noted that difficulties with OB rotation reflect the need to maintain the spatial relationships within the array, which may not be solely required during VPT tasks (Lambrey, Doeller, Berthoz, & Burgess, 2012). Indeed, during VPT tasks, adults may have the additional potential of coding the static locations of array objects in relation to external landmarks whilst updating one's egocentric reference frame, leading to enhanced performance compared to OB rotations (Burgess, Spiers, & Paleologou, 2004).

2.1.2 Development of OB rotation and VPT abilities

The emergence of mental rotation abilities across development has also been examined. Piaget and Inhelder (1971) suggested that children develop the ability to solve VPT and OB mental rotation tasks at different ages, with the ability to perform OB tasks by 7-8 years and successful performance on VPT tasks developing later at 9-10 years. Piaget concluded that this difficulty in VPT tasks was partly a consequence of the child's preponderance to respond 'egocentrically' (i.e., continuing to give an answer to a rotation task that is identical to that of their current position). However,

performance on VPT tasks in children differs depending on the way in which such tasks are framed (for a review, see Newcombe & Frick, 2010). For instance, Successful performance is observed earlier in development (around 4 years) if the child is asked to identify whether an individual who is standing at another location can see a given object, than if they are asked to state what a scene would look like from an alternative viewpoint (with success by 8-10 years of age) (Gzesh & Surber, 1985; Salatas & Flavell, 1976). Newcombe and Huttenlocher (1992) also found that 3 and 4 year-olds could succeed on VPT tasks when given questions that were related to identifying the locations of specific items from non-occupied perspectives, rather than asking participants to match alternative viewpoints from a range of pictures.

Using a reaction time test, Marmor (1975) found that children as young as 5 years are able to succeed on OB mental rotation tasks, and by 8 years are able to perform almost at an adult level. In line with adult data (e.g., Shepard & Metzler, 1971; Zacks et al., 2002), reaction times were found to be slower for an increased angle of rotation for 5- and 8-year-olds. Others have similarly indicated that children start to use OB mental rotation between 4 and 6 years (Estes, 1998; Kosslyn, Margolis, Barrett, Goldknopf, & Daly, 1990). Together, these studies suggest that OB and VPT abilities emerge earlier than originally thought, with both becoming available from approximately four years of age.

Roberts and Aman (1993) argued, however, that children below the age of 7 years are not fully competent on VPT tasks. That is, when determining left-right directions from non-occupied positions they tend to respond in line with, and 'over-extend', their stationary egocentric left-right reference frames. In children aged 7-8 years, who were more able to correctly determine left-right directions from a non-occupied position, a linear increase in reaction time was found with greater angularity between real and imagined viewpoints. This is in contrast to typical adults, who do not demonstrate an angular discrepancy effect in VPT tasks (Wraga et al., 2000; Zacks et al., 2000), and indicates that children may use a different technique, such as graduated imagined rotation of the self, whilst adults may be more able to use the relationships

between items in the array and external landmarks to support a more automatic updating of their body-based frame of reference (Wraga et al., 2000).

Xistouri and Pitta-Pantazi (2006) also found a significant difference in the performance of children aged 9- and 12-years on a VPT task, demonstrating enhanced ability to rotate one's egocentric frame of reference with increasing age. Similarly, Epley and colleagues (Epley, Morewedge, & Keysar, 2004) found that young children interpret VPT instructions egocentrically and have difficulty in rotating this frame of reference in order to complete these tasks. Interestingly however, they also found that adults initially interpret instructions egocentrically, but have a superior ability to adjust to using an appropriate strategy quickly and effectively. Correspondingly, difficulties in inhibiting an egocentric response until later in development are likely related to protracted maturation of executive control (Diamond, 1990).

2.1.3 Neurological distinction between OB rotations and VPT

As mentioned in chapter 1, despite high correlations between performance on OB and VPT transformation tasks in adults (Hegarty & Waller, 2004), a measurable distinction between these transformation types has been demonstrated by neuroimaging data (e.g., Kosslyn, DiGirolamo, Thompson, & Alpert, 1998; Wraga, Shephard, Church, Inati, & Kosslyn, 2005; Zacks et al., 2000; Zacks et al., 2002; Zacks et al., 1999). For instance, Zacks, Vettel, and Michelon (2003) found that rotations of items in an array (OB) were associated with preferential activity in right interparietal sulcus and decreased activity in left temporo-parietal junction and superior temporal sulcus. Imagined rotations of the self (VPT), conversely, were associated with increased activation of left parieto-temporo-occipital junction and superior temporal sulcus. More recently, when comparing a VPT with an OB task, Lambrey et al. (2012) found significantly greater activation of the parieto-occipital sulcus, including the retrosplenial cortex, and areas such as the left anterior hippocampus in VPT than OB rotation tasks. These areas are thought to be involved in transforming between egocentric to allocentric spatial representations (Vann, Aggleton, & Maguire, 2009), which may be important for

successful imagined self-rotations. Thus, this region may be associated with an ability to update egocentric spatial locations (supported by the posterior parietal lobe) within an allocentric frame of reference (supported by hippocampal and medial temporal lobe structures) during VPT tasks (Lambrey et al., 2012).

Neuroimaging research in WS has found a number of structural and functional abnormalities in cortical regions associated with visual-spatial processing. In particular, impairment of the superior parietal lobule has been identified in WS (Eckert et al., 2005), a region associated with OB rotation (e.g. Podzebenko et al., 2002). Furthermore, atypical metabolism and function of the anterior hippocampus (Meyer-Lindenberg et al., 2005), and decreased parieto-occipital grey-matter concentration (Boddaert et al., 2006) have also been identified. Given the role of these cortical regions in the spatial updating of one's viewpoint following actual and imagined rotation (Burgess, 2008; Vann et al., 2009), individuals with WS are likely to show poor performance on associated tasks. Therefore, although atypical dorsal stream functioning may go some way to explaining mental rotation difficulties in WS (J. Atkinson et al., 2003; Stinton et al., 2008), atypical processing and functioning of more widespread structures and their intercortical connectivity may further explain the specific pattern of spatial deficits observed in this disorder.

2.1.4 OB and VPT abilities in WS

To date, only a handful of studies of visuospatial abilities in WS have included tests of OB mental rotation (e.g., Farran et al., 2001; Vicari et al., 2006) (although see 1.5.2 for a more detailed review of the literature). Research into VPT abilities in WS and how performance across different spatial transformation tasks compares with that of TD individuals is also limited. In one study, Farran et al. (2010) asked individuals with WS to state whether a picture of an animal placed between themselves and the examiner would appear the right-way-up or upside-down from the viewpoint of the examiner. Results yielded chance performance in the WS group, although questions only examined imagined self-rotation by 180°.

Detailed examination of performance on both OB and VPT tasks, which require imagined, rather than actual movement in WS, may provide further insight into the specific pattern of difficulties, and subsequently allow clearer conclusions to be drawn as to the nature of different aspects of visuospatial processing in this group. The aim of this study was to therefore examine performance on OB and VPT tasks in individuals with WS compared to TD children between 5 and 10 years of age, and to examine changes in performance with increasing degrees of rotation across groups. OB rotation tasks can either require an individual to imagine the rotation of a single object, or the rotation of an array of objects, and these are likely to rely on shared underlying mechanisms (Lambrey et al., 2012). Similarly, VPT tasks can be separated into those that require the individual to imagine a displacement of the self to an unoccupied viewpoint around an array, or to imagine the rotation of the self within an array. Despite the overlapping underlying mechanisms involved in the two types of OB rotation and two VPT rotations, there may be different levels of difficulty and ranges in sensitivity across such tasks. As such, this study used four separate rotation tasks (two OB and two VPT tasks) with the purpose of examining this range of abilities across each group.

2.2 Method

2.2.1 Participants

Sixty-eight typically developing (TD) children were recruited from three London primary schools. Twenty-one participants with Williams Syndrome (WS) were recruited from the records of the Williams Syndrome Foundation, UK. All WS participants had received a positive diagnosis of WS, based on a "fluorescence *in-situ* hybridisation" (FISH) test for deleted Elastin gene on chromosome 7, and phenotypic diagnosis by a clinician. All TD participants were tested in a quiet room within their schools, whilst WS participants were tested either at their home or in a testing room at the Institute of Education, London. Written informed consent was obtained from the

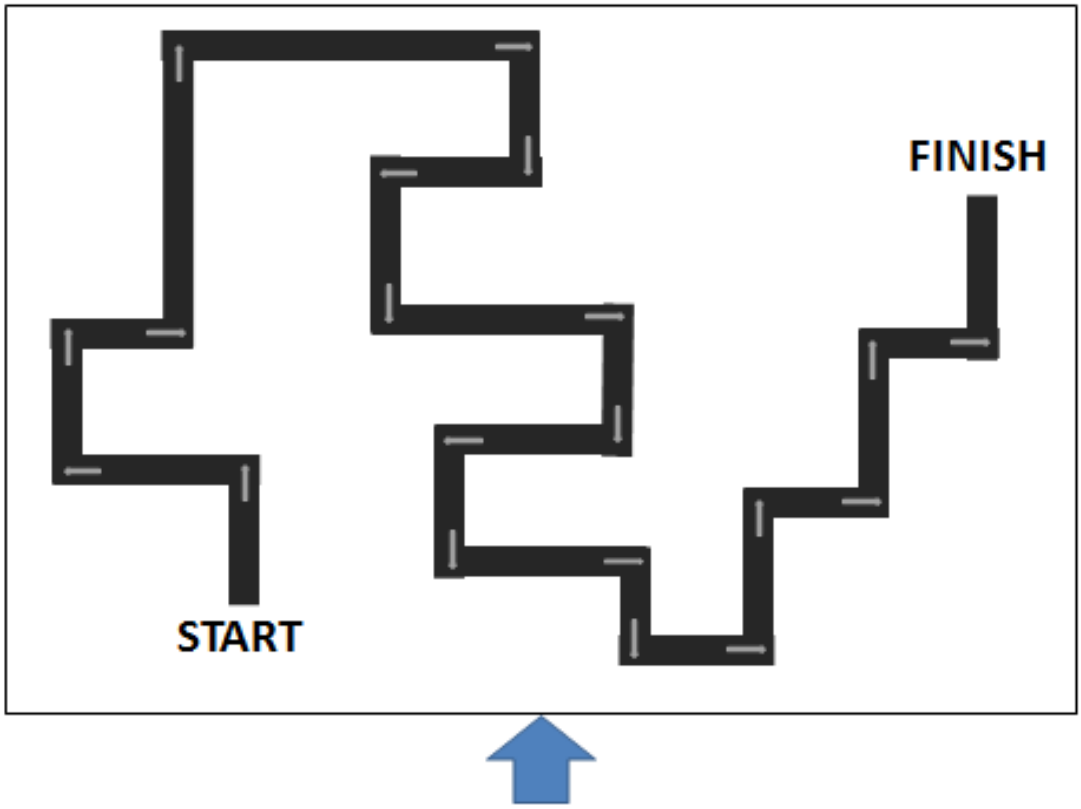
parents of all participants, and signed individual consent from participants with WS over 12 years of age.

Due to difficulties in concentration, one TD 5 year-old and one WS participant were subsequently excluded from the analyses. For analyses of performance across development, participants were separated into four TD age-groups; 5 years (N=16, 8 males, Mean age (years; months) = 5;06, SD= 0;04, CA range = 5;01 – 6;01), 6 years (N=17, 11 males, M_{age}= 6;08, SD= 0;03, CA range = 6;02 – 7;05), 8 years (N=18, 10 males, M_{age}= 8;03, SD= 0;05, CA range = 7;07 – 8;09), and 10 years (N=16, 9 males, M_{age}= 10;01, SD= 0;03, CA range = 9;06 – 10;09) and compared to the WS group (N=20, 10 males, M_{age}= 24;04, SD=10;06, CA range = 13;01 – 46;01). Verbal and non-verbal abilities were assessed using the British Picture Vocabulary Scale-III (BPVS-III; Dunn, Dunn, Styles, & Sewell, 2009) and the Ravens Coloured Progressive Matrices (RCPM; Raven, Raven, & Court, 2003), respectively.

2.2.2 Visual perspective-taking (VPT) Path

The VPT path task was conducted to examine body-based rotation abilities. In this task, participants were sat in front of a 2D map-like route presented on an A4 piece of paper on a table in front of them (2.2.2.1 Figure 1). Participants were asked to imagine walking the route from start to finish. Along the route were 20 decision points, with 10 left turns, and 10 right turns. The route consisted of 5 turns at no imagined rotation (0°), 10 turns in which the participant must imagine themselves at 90° from their actual vantage point, and 5 turns at 180° (imagining looking directly behind their actual view). At each turn the participant stated whether they would turn their body to the left or the right to continue down the path. Given that young children and some individuals with WS have difficulties distinguishing their left from right sides (Landau & Hoffman, 2005), each participant was given a sticker on one hand (randomised left and right across participants) so that instead of declaring a left or right turn, they stated whether they would turn to their 'sticker' or 'no-sticker' side. This was similar to a

method used by Newcombe and Huttenlocher (1992) with TD 3 and 4 year olds, which significantly improved performance on such tasks.



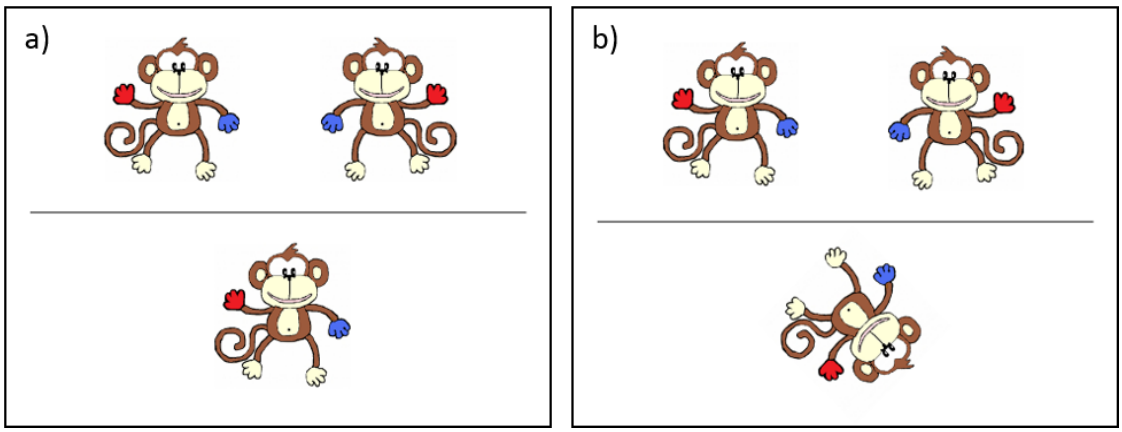
2.2.2.1 Figure 1. Visual perspective-taking (VPT) path task

2.2.3 Object-based (OB) monkey mental rotation

The OB monkey task was used to examine the ability to mentally rotate a single image, based on the classic mental rotation paradigms used by Shepard and Metzler (1971) and Marmor (1975). Participants were asked to view two cartoon monkeys above a horizontal line and one monkey below the line at varying degrees of rotation from upright (see 2.2.3.1 Figure 2). Stimuli were presented on a 14" laptop computer screen. Participants were asked to choose which of the two monkeys on the top matched the one underneath. The monkeys all had one red hand pointing upwards above a tail, and one blue hand pointing downwards. The incorrect monkey was always a mirror-image of the correct monkey so that verbal coding could not be used to solve the task (e.g., red hand is next to the tail). Participants indicated their response by

pressing either the designated left button (covering keys 'A, S, D, Z, and X') or right button (covering keys 'J, K, L, M and ,') on the keyboard in front of them.

The monkey task consisted of six practice trials (to indicate whether the participant understood the task) and 32 experimental trials (4 x 0° trials, 8 x 45° trials, 8 x 90° trials, 8 x 135° trials, and 4 x 180° trials). The 0° condition was used to indicate whether the participant understood the instructions and was able to correctly visually match the two correct monkeys. The test positions of the target monkey were 45°, 90°, 135° and 180° clockwise rotations and -45°, -90°, -135° anticlockwise rotations. For counterbalancing, half of the trials included a target monkey with the red hand to the right, and half with the target as the mirror image (red hand to the left). Participant reaction times and number of correct trials for each degree of rotation from 0° were recorded.



2.2.3.1 Figure 2. Object-based (OB) monkey mental rotation task: a) 0º control condition, b) 135º clockwise rotation condition

2.2.4 Visual perspective-taking (VPT) circle

The design of the VPT circle task was based on Newcombe and Huttenlocher (1992) and used to examine the ability to imagine the self rotating around an array. In contrast to Newcombe and Huttenlocher (1992), a circular board was used instead of a square board to present the array of objects. This controlled for the use of a frame of

reference based on aligning the four sides of the board with the walls of the room or edges of the table (Kelly & McNamara, 2010; Shelton & McNamara, 2001).

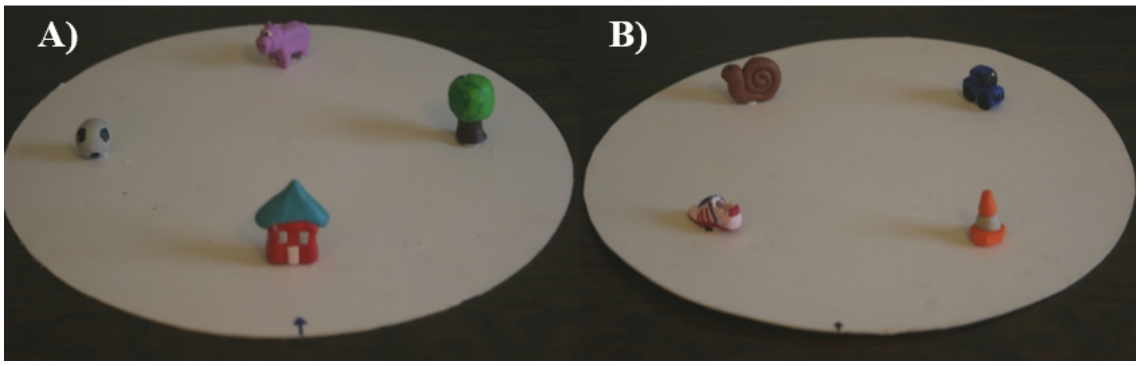
Participants were positioned in front of one of two white 13" circular arrays (A or B, see 2.2.4.1 Figure 3) of four 3D coloured clay objects. Array A) contained a pig, a tree, a house, and a football. Array B) contained a snail, a car, a traffic cone and a shoe. Participants were first asked to name each object to demonstrate that they knew the correct word for each and that each object was equally recognisable.

Throughout the task, the participant was asked to imagine looking at the array from different viewpoints and asked a series of questions about the position of the different objects from the imagined perspectives. For each imagined rotation condition, participants were asked "imagine you are standing here and looking this way (a red arrow was placed on the table to indicate imagined direction of gaze), which object is a) closest to you, b) furthest away from you, c) to your left and d) to your right. Questions were presented in blocks for each rotation, but the order of questions varied randomly for each trial.

All participants were tested on both arrays (A and B, separately) to measure mental rotation abilities at a variety of imagined displacements (45°, 90°, 135° and 180°, collapsed across clockwise and anti-clockwise rotations). Two different arrays of objects were used as opposed to one array so that all orientations could be measured without introducing a high cognitive load of having too many objects on one array. Array A therefore allowed for imagined self-rotations of 90° and 180°, and Array B, for rotations of 45° and 135°. The order of presentation of the two arrays (A or B first) was counterbalanced across participants.

The test consisted of 32 trials (16 trials for each array): four 0° (control), eight 90° rotation trials, four 180° rotation trials, eight 45° rotation trials and eight 135° rotation trials. Therefore, this differed from the task used by Newcombe and Huttenlocher (1992) by including a greater number of angles of rotation, allowing for an analysis of the changes in the number of errors with increased rotation from 0°. In addition, in the same way as in the VPT path task, one hand of each child was marked

with a sticker in order that they did not have to use the terms ‘left’ and ‘right’, which could have introduced a confound. Instead, participants referred to their ‘sticker side’ and ‘no-sticker side’.



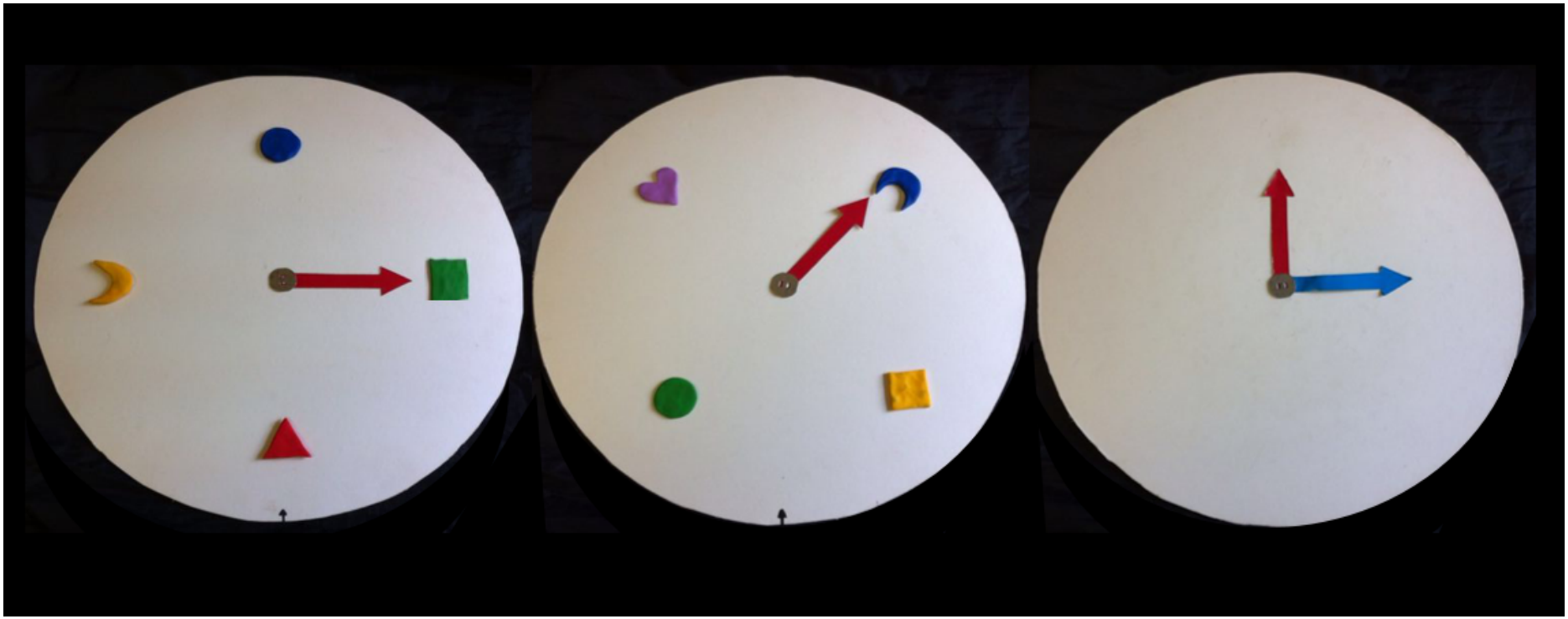
2.2.4.1 Figure 3. Visual perspective-taking (VPT) circle task: A) for imagined rotations of 90° (standing in front of the tree or football), 180° (in front of the pig), or 0° control condition (in front of the house); B) for imagined rotations of 45° (in front of the shoe or traffic cone) and 135° (in front of the car or snail).

2.2.5 Object-based circle

Participants were positioned in front of an array (A or B, see 2.2.5.1 Figure 4) of four coloured shapes. Participants were shown a central red arrow pointing towards one of the shapes in the array (e.g. a blue moon). The participant was asked to imagine that the whole array was turned until the red arrow was pointing upwards and the object it was pointing to (e.g. the blue moon) was pointing at the top. They were then asked to indicate in turn (using array C, see 2.2.5.1 Figure 4) where the other three objects would have moved to, given this rotation. For example, the participant was asked “If I were to turn the circle of shapes around so that the red arrow is now pointing upwards and the blue moon is at the top, can you point the blue arrow to show me where the yellow square has moved to?” Participants then moved the blue arrow on the blank circular board (C) to the required position.

Across the two arrays (A and B), participants could be tested on the same degrees of mental rotation as in the VPT circle (45°, 90°, 135°, and 180°, collapsed

across clockwise and anti-clockwise rotations). This test consisted of 24 trials: three at 0° (control), six at 45° rotations, six 90° rotation trials, six 135° rotations, and three 180° rotation trials. The 0° control condition was used to determine whether the participant understood the instructions (e.g. that the blue arrow on the blank circle must point towards the position of the target object within array, despite the absence of the shapes). A pilot study with six TD 5 year-olds showed that it was important to first demonstrate an actual rotation of the board so that the participant could grasp the concept of the whole array rotating. This was done by briefly rotating array A to 45° clockwise and then anticlockwise whilst the experimenter said, "Look at what happens when I turn the circle, all the shapes move around". This small degree of rotation was chosen so that participants could not use their memory for the final location of shapes on experimental trials for this array.



2.2.5.1 Figure 4. Object-based (OB) circle task: A) imagined rotations of 90 (red arrow to green square or yellow moon) and 180 (red arrow to red triangle), B) imagined rotations of 45° (red arrow to blue moon or pink heart) and 135° (red arrow to yellow square or green circle); C) answer circle where participants move only the blue arrow to indicate where the other objects would move to following imagined rotations.

2.2.6 Order of task presentation

All participants completed the BPVS-III and RCPM before any mental rotation measures. Participants then received either the VPT path task or OB monkey task (counterbalanced across participants), followed by the two circle tasks. The OB circle task was always conducted before the VPT circle as participants who are given a perspective-taking task first, have been found to make fewer errors on subsequent object-based tasks of similar content, but not vice-versa (Pellizzer, Bâ, Zanello, & Merlo, 2009). All tasks were completed on the same day, with breaks given where necessary. Total testing time was approximately 45 minutes. However, when shorter testing sessions were required, two sessions were used (session 1: BPVS-III, RCPM; session 2: rotation tasks) spaced less than one month apart (Mean = 16.28 days [SD = 16.99]).

2.3 Results

2.3.1 BPVS-III and RCPM

BPVS-III and RCPM data for WS and TD groups were normally distributed (Kolmogorov-Smirnov, $p > .05$). Analyses of variance (ANOVAs) were conducted separately for BPVS and RCPM scores, each with group (5 levels; 5y, 6y, 8y, 10y, and WS) as a between-subjects factor (see 2.3.1.1 Table 2). This demonstrated an uneven cognitive profile in WS, characteristic of the disorder (Jarrold et al., 1998), with nonverbal abilities at a level no different from TD 5 and 6 year-olds and relatively higher verbal abilities at the level of TD 8 and 10 year-olds.

2.3.1.1 Table 2. Mean (SD) participant scores on BPVS-III and RCPM.

	Group					ANOVA		Post-hoc[a]
	WS (N=20)	5 years (N=16)	6 years (N=17)	8 years (N=18)	10 years (N=16)	F (df)	*p*	
BPVS raw[b]	123.50 (22.09)	81.69 (15.86)	91.47 (13.53)	112.67 (15.37)	130.81 (15.18)	25.53 (4, 86)	< *.001*	5 = 6 < 8, 10, WS 8 < 10 WS = 8 and 10
BPVS stand[c]	-	100.94 (10.98)	95.06 (10.92)	102.78 (14.57)	97.44 (12.92)	1.32 (3, 66)	.275	-
RCPM[d]	18.05 (4.56)	19.62 (4.50)	23.65 (4.99)	28.12 (4.89)	30.38 (3.12)	24.29 (2, 85)	< *.001*	5 = 6 < 8 = 10 WS < 6, 8, 10

[a] Tukey-corrected post-hoc tests, '=' refers to no significant difference at .05 level, and '<' denotes $p < .01$; [b] BPVS-III: British Picture Vocabulary Scale-III raw scores, [c]BPVS-III standardised scores; [c] RCPM: Ravens Coloured Progressive Matrices (RCPM) raw scores

2.3.2 Visual perspective-taking (VPT) path

Given the different number of trials across each degree of rotation within the VPT path task (5 rotations at 0°, 10 rotations at 90° and 5 rotations at 180°), total correct responses for each rotation were converted to percentage scores for analysis across groups. For Mean percentage correct for each rotation across groups, see 2.3.2.1 Figure 5a.

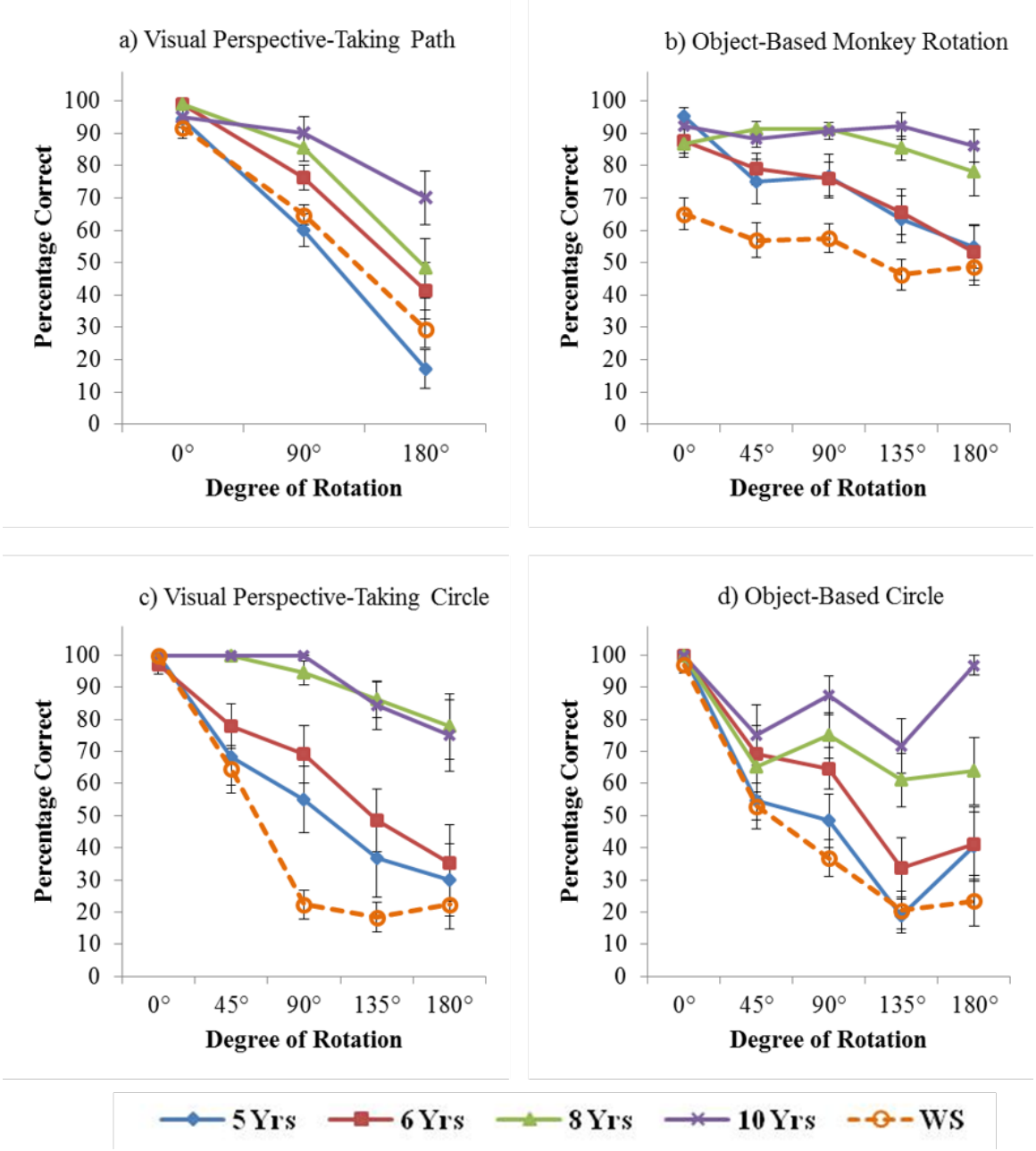
Data were non-normally distributed for half of the variables in the TD and WS groups (Kolmogorov-Smirnov, $p< .05$). However, given the similar group sizes, lack of outliers in the data and that ANOVA can be robust to violations of normality assumptions, the results of parametric tests are reported. Non-parametric equivalents of the following analyses were also conducted, with comparable results.

To examine whether the performance in each group differed from chance (50%) on VPT path rotation trials, one-sample t-tests were conducted on the data. On 90° trials, all groups except 5 year-olds scored significantly above chance: 6 years, $t(15) = 7.00$, $p < .001$; 8 years, $t(16) = 8.75$, $p < .001$; 10 years, $t(15) = 8.137$, $p < .001$; WS, $t(18) = 4.62$, $p < .001$), and on 180° trials the 5 year-olds, $t(13) = -5.591$, $p < .001$, and WS groups, $t(18) = -3.54$, $p = .002$, scored significantly below chance, indicating the consistent use of a disadvantageous strategy at this angle of rotation in these two groups. Ten year-olds were the only group to score significantly above chance on 180° trials, $t(15) = 2.45$, $p = .027$. Given this pattern of some groups performing above and others below chance, data were analysed further to examine group differences.

A mixed ANOVA, with group as a between-participant factor (5 levels: 5y, 6y, 8y, 10y, and WS) and rotation as within-participant factor (3 levels: 0°, 90°, and 180°) was conducted on the data. Assumptions of sphericity were violated (Maulchley's, $p < .05$); therefore Greenhouse-Geisser corrected tests are reported ($\varepsilon = .68$). There was a significant main effect of group, $F(1, 77) = 10.60$, $p < .001$, partial $\eta^2 = .36$, with Tukey post-hoc tests showing that the WS group scored below 8 and 10 year-olds ($p = .010$ and $p < .001$, respectively), and 5 year-olds scored below 6, 8 and 10 year-olds ($p = .033$, $p = .001$ and $p < .001$, respectively). A significant main effect of rotation was also found, reported as a linear contrast, $F(1, 77) = 216.19$, $p < .001$, partial $\eta^2 = .74$, with Tukey-corrected pairwise comparisons revealing significant differences between all degrees of rotation ($p < .001$ for all).

There was also a significant group by rotation interaction, $F(8, 154) = 3.74$, $p = .003$, partial $\eta^2 = .16$. To further examine the effect of rotation in each group, repeated measures ANOVAs were conducted (see 2.3.2.2 Table 3), showing least detriment with degree of rotation in TD 10 year-olds. To examine differences between rotation trials across groups, one-way ANOVAs were conducted. There was a significant difference across groups at 90°, $F(4, 81) = 9.47$, $p < .001$, and 180° rotations, $F(4, 81) = 6.37$, $p < .001$, with Tukey post-hoc tests revealing at 90°, 5 and WS scored

significantly below 8 and 10 year-olds ($p < .05$), and at 180°, 5 and WS scored significantly below 10 years ($p < .05$).



2.3.2.1 Figure 5. Mean (SE) percentage correct at each degree of rotation across TD and WS groups on each mental transformation task, a) VPT path, b) OB monkey task, c) VPT circle task, d) OB circle task

2.3.2.2 Table 3. Statistical analyses of effect of rotation in each group on VPT path task

	F	*df*	*p*	Partial η^2	Post-hoc[a]
WS	87.27	(1,18)	*<.001*	.83	0°>90°>180°
5 years	114.18	(1,13)	*<.001*	.89	0°>90°>180°
6 years	43.36	(1,15)	*<.001*	.74	0°>90°>180°
8 years	28.89	(1,16)	*<.001*	.64	0°>90°>180°
10 years	7.98	(1,15)	*<.001*	.35	0°>180°

[a]LSD pairwise comparisons, '>' denotes 'significantly greater percentage correct', at .05 level.

2.3.3 OB monkey mental rotation

2.3.3.1 Percentage correct.

To examine differences across groups on number of correct responses in the monkey mental rotation task for each degree of rotation from upright, data were collapsed across equivalent clockwise and anti-clockwise degrees of rotation (e.g. collapsed all 45° and -45° rotation trials). As the total number of trials differed for each degree of rotation (4 x 0° trials, 8 x 45° trials, 8 x 90° trials, 8 x 135° trials, and 4 x 180° trials), the Mean percentage of correct responses for each rotation was calculated. Following difficulties in completing the task correctly, one TD 6 year-old and one TD 8 year-old was excluded from the analyses.

For percentage of correct responses for each group across increasing degree of rotation, data met assumptions for normality for all variables in the WS group (Kolmogorov-Smirnov, *p> .05*), but not for the TD groups (*p< .001*). However, given the similar group sizes, lack of outliers in the data and that ANOVA can be robust to violations of normality assumptions parametric analyses are reported. Non-parametric equivalents for main effects of the following analyses were also conducted, with comparable results. For percentage of correct scores for each degree of rotation in each group, see 2.3.2.1 Figure 5b.

To examine whether performance in each group differed from chance (50%), one-sample t-tests were conducted. Results yielded significant above-chance performance in each TD group for 45° trials: 5 years, $t(15)= 3.65$, *p=.002*; 6 years, $t(15)= 5.71$, *p< .001*; 8 years, $t(16)= 17.59$, *p< .001;* and 10 years, $t(15)= 14.35$, *p< .001*, and 90° trials: 5 years, $t(15)= 3.94$, *p=.001*; 6 years, $t(15)= 4.77$, *p< .001*; 8 years, $t(16)= 19.79$, *p< .001;* and 10 years, $t(15)= 15.18$, *p< .001*. However, only 8 and 10 year-old TD children performed significantly above chance on 135° trials, $t(16)= 9.41$, *p<.001* and $t(15)= 9.93$, *p< .001*, respectively; and 180° trials, $t(16)= 3.78$, *p= .002* and $t(15)= 7.06$, *p< .001*, respectively. In contrast to VPT path results, the WS group did not score significantly differently from chance on any rotation trials (*p> .013* for all), despite performing reliably above chance on 0° control trials, $t(19) = 3.04$, *p= .007*; demonstrating an ability to understand the task.

A two-way mixed ANOVA was conducted with a between-participant factor of group (5 levels: 5y, 6y, 8y, 10y, and WS) and within-participant factor of rotation (5 levels: 0°, 45°, 90°, 135°, and 180°). Assumptions of sphericity were violated (Mauchley's, *p< .05*), therefore Huynh-Feldt corrected tests are reported (*ε = .82).* Results showed a significant main effect of group, $F(4, 80) = 14.60$, *p< .001,* partial $\eta^2 = .42$, with post-hoc Tukey tests showing that the WS group scored significantly below all TD groups (*p< .01* for all). In addition, 5 and 6 year-olds scored below 10 year-olds (*p= .015* and *p= .023*, respectively), and no differences were found between any other TD groups (*p> .05* for all).

There was also a significant main effect of rotation, $F(4, 320) = 19.92$, *p< .001*, partial $\eta^2 = .19$. Post-hoc tests showed a greater percentage correct at 0° compared to 45°, 135° and 180° (*p< .01* for all). A greater percentage correct was also found for 45° trials compared to 135° and 180° (*p< .01* for both), and for 90° compared to 135° and 180° (*p< .01* for both). No other significant differences were found (*p> .05*).

A significant group by rotation interaction was also found, $F(16, 320) = 2.49$, *p= .002,* partial $\eta^2 = .11$. To examine this pattern further, repeated measures ANOVAs for the effect of rotation were conducted for each group separately (see 2.3.3.1.1 Table

4), showing an effect of rotation in the younger TD and the WS groups only, although significant differences between levels of rotation did not remain following pairwise comparisons in the WS group.

One-way ANOVAs found a significant difference across groups at each degree of rotation ($p = .001$, for all). Post-hoc tests found that on 0° trials WS group scored below all groups ($p < .05$); on 45° trials WS scored below 6, 8 and 10 year-olds ($p < .05$); on 90° trials WS group scored below all TD groups ($p < .05$); on 135° trials 5 and 6 year-olds scored below 10 year-olds ($p < .05$), and WS were below 8 and 10 year-olds ($p < .05$); and on 180° trials 5 and 6 year-olds scored below 10 year-olds, and WS were below 8 and 10 years ($p < .05$ for all).

2.3.3.1.1 Table 4. Statistical analyses of effect of rotation in each group on OB monkey task

	F	*df*	*p*	Partial η^2	Post-hoc[a]
WS	11.75	(1,19)	=*.003*	.38	0°> 135° and 180°; 90° > 135°
5 years	50.68	(1,15)	<*.001*	.77	0°> all; 45°> 135° and 180°; 90°> 180°
6 years	16.41	(1, 15)	=*.001*	.52	0° and 45°> 135° and 180°; 90° > 135° > 180°
8 years	1.56	(1, 16)	=*.230*	.09	-
10 years	.46	(1, 15)	=*.510*	.03	-

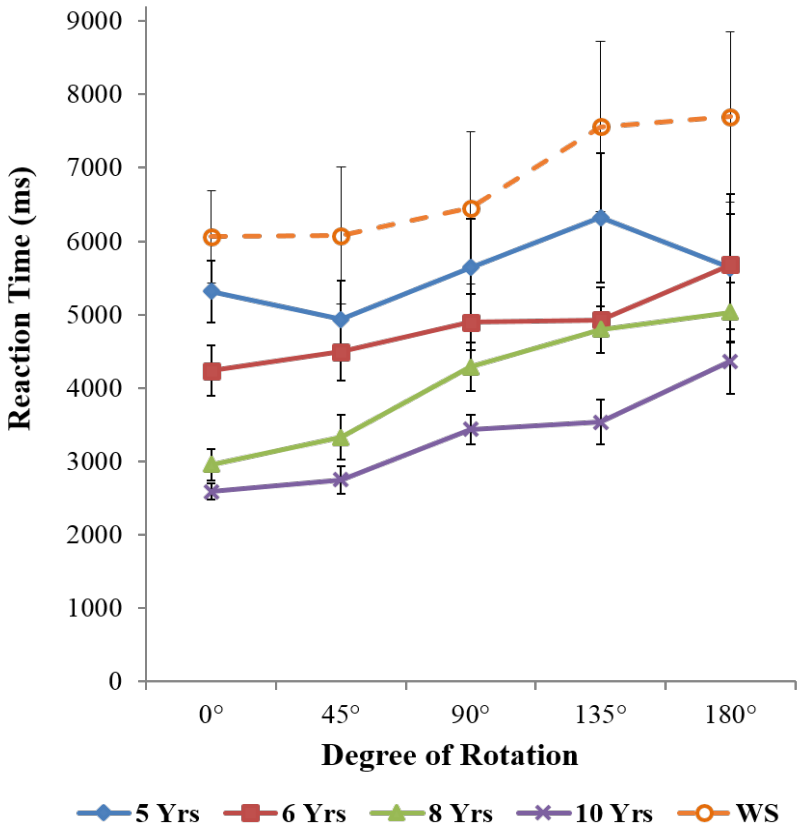
[a]LSD pairwise comparisons, '>' denotes 'significantly greater percentage correct', at .05 level.

2.3.3.2 Reaction times (RT).

For Mean RT for each degree of rotation across groups, see 2.3.3.2.1 Figure 6. Data were normally distributed for four out of five variables in both TD and WS groups (Kolmogorov-Smirnov; $p > .05$). Therefore parametric analyses were performed on the

data. A mixed ANOVA, with group as a between-participant factor (5 levels: 5y, 6y, 8y, 10y, and WS) and degree of rotation as a within-participant factor (5 levels: 0°, 45°, 90°, 135°, and 180°) was conducted. Assumptions of sphericity were violated (Maulchley's, $p < .05$); therefore Greenhouse-Geisser corrected tests are reported ($\varepsilon = .74$). This showed a significant main effect of group, $F(4, 76) = 6.59$, $p < .001$, partial $\eta^2 = .26$. Tukey-corrected post-hoc tests found significantly slower RTs for WS compared to 8 and 10 year-olds ($p = .003$ and $p < .001$, respectively). No significant differences in RT were found between any other groups *(p> .05)*. There was also a significant main effect of rotation, $F(4, 304) = 11.90$, $p < .001$, partial $\eta^2 = .14$. Pairwise comparisons found faster RT for 0° compared to 90°, 135°, and 180° ($p < .010$ for all); for 45° compared to 90°, 135°, and 180° ($p < .05$ for all); and for 90° compared to 180°.

In contrast to the scores for percentage correct, there was no significant group by rotation interaction ($F<1$), suggesting that although the performance in the WS and youngest two TD groups declined with increasing degrees of rotation, the same groups did not necessarily respond proportionally more slowly with increased rotation.



2.3.3.2.1 Figure 6. Mean (SE) reaction times for each degree of rotation on the object-based (OB) monkey rotation task in each group

2.3.4 Visual perspective-taking circle

2.3.4.1 Percentage correct.

On control trials from own vantage point (no rotation), almost all participants performed perfectly, with only four participants making one error each (two 6 year-olds, one 10 year-old and one participant with WS). One WS and one TD 5 year-old were unable to pass the control phase and were therefore not included in subsequent analyses.

Correct responses could be divided into near-far trials (naming objects nearest and furthest, following imagined rotations) and left-right trials (naming objects to the left and right of the self, following imagined rotations). To examine differences in performance on near-far compared to left-right trials, t-tests were conducted for WS and TD groups separately. In both groups, participants showed significantly stronger performance on near-far than left-right trials; TD, (Mean near-far = 92.86%, Mean left-

right = 74.24%), t(65) = 5.527, p< .001; and WS, (Mean near-far = 59.77%, Mean left-right = 33.45%), t(18) = 5.257, p< .001. This could suggest that near-far trials are easier than left-right trials. However, we suggest that responses on near-far trials could have been based on an alternative strategy that does not require mental rotation. That is, participants might have made spatial judgements based on their understanding of distances between the target object and direction arrow, rather than using mental rotation. To ensure that the data entered into analysis was a pure measure of mental rotation, all subsequent analyses on this task examined the effect of rotation on left-right trials only, as these could not be completed by an alternative strategy; these trials required the use of left-right body coordinates following imagined rotation of the self.

Left-right trials were divided by degree of rotation (4 levels: 45°, 90°, 135° and 180°), with data collapsed across equivalent clockwise and anti-clockwise degrees of rotation (e.g. imagined rotations -90° to the left and 90° to the right) for analysis. For percentage correct on left-right trials across groups on the VPT circle task, see 2.3.2.1 Figure 5c.

Data showed that 8 and 10 year-olds scored highly across the task and were not affected by rotation, with ceiling performance on 0°, 45° and 90° trials. In comparison, the 5 and 6 year-olds showed a decline in performance with increased rotation, and the WS group showed very poor performance on all rotation trials above 45°.

To examine whether the performance in each group differed significantly from chance (25%), one-sample t-tests were conducted on the data. Results indicate that, similar to performance on the OB monkey task, all TD groups scored significantly above chance on 45° trials: 5 years, t(14)= 4.84, *p< .001*; 6 years, t(16)= 7.49, *p< .001*; 8 and 10 year-olds scored 100% correct. The WS group also scored significantly above chance on 45° trials, t(18)= 5.11, *p< .001*. On 90° trials, only 6, 8, and 10 year-olds scored significantly above chance: 6 years, t(16)= 4.92, *p< .001*; 8 years, t(17)= 18.22, *p< .001;* 10 year-olds scored 100% correct. Only 8 and 10 year-old TD children performed significantly above chance on 135° trials: t(17)= 11.25, *p<.001* and t(15)= 7.889, *p< .001*, respectively, and 180° trials: t(17)= 5.23, *p< .001* and t(15)= 4.47,

p< *.001*, respectively. Scores in the WS group however, were not significantly different from chance for 90°, 135° or 180° trials (*p*> *.013* for all).

The data did not meet assumptions for normality for any variables in TD or WS groups (Kolmogorov-Smirnov, p< .01). Therefore, data for each group were analysed using non-parametric tests. Kruskal-Wallis test was carried out on percentage correct for left-right responses with a participant factor of group (5 levels: 5, 6, 8, 10 and WS) collapsed across all rotation trials and also for each degree of rotation separately. There was a significant difference across groups on percentage correct on all rotation trials (H(4) = 50.62, *p*< *.001*). No significant difference was found across groups on 0° trials (H(4) = 4.00, *p*= *.406*), suggesting that all groups understood the task.

Mann-Whitney post-hoc tests revealed that on 45° trials, the 5 and 6 year-olds and WS groups performed more poorly than the 8 and 10 year-old groups (*p*<*.05* for all). All other comparisons at 45° were not significant (*p*>*.05*). On 90° trials, 5 year-olds scored below 8 and 10 year-olds (*p*= *.001*), 6 years below 10 year-olds (*p*< *.005*), and WS below 6, 8 and 10 year-olds (*p*< *.001* for all). On 135° trials, 5 and 6 year-olds and WS groups performed significantly below 8 and 10 year-olds (*p*< *.005* for all). On 180° trials, results demonstrated that 5 year-olds performed more poorly than 8 year-olds (*p*< *.005*), and WS were reliably below 8 and 10 year-olds (*p*< *.001*).

To examine the effect of rotation further, Friedman's ANOVAs with a within-participant factor of degree of rotation (5 levels: 0°, 45°, 90°, 135°, 180°) were conducted for all groups together, yielding a significant effect of degree of rotation, $\chi^2(4) = 118.64$, *p*< *.001*, due to fewer correct responses for increasing degrees of mental rotation. Analyses for each group separately are displayed in 2.3.4.1.1 Table 5.

2.3.4.1.1 Table 5. Statistical analyses of effect of rotation in each group on VPT circle task

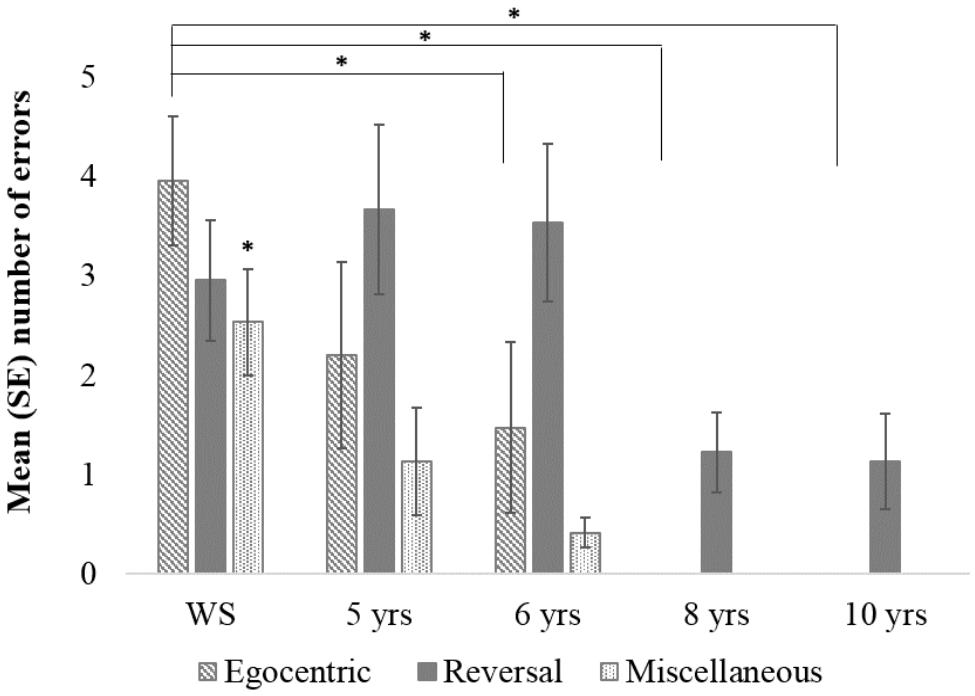
	χ^{2a}	*df*	*p*	Post-hoc[b]
WS	48.21	4	*<.001*	0°> all
5 years	24.82	4	*<.001*	0°>90°,135°,180°
6 years	31.41	4	*<.001*	0°>90°>135°,180°; 45°>135°,180°
8 years	11.40	4	*=.022*	NS
10 years	14.57	4	*=.006*	NS

[a]Results of non-parametric Friedman's ANOVA; [b]Wilcoxon pairwise comparisons. 'NS' denotes 'no significant differences following pairwise comparisons (.01 significance level)'

2.3.4.2 Types of errors on VPT circle task.

The different types of errors made on the VPT circle task were analysed to examine differences in strategies used and whether specific aspects of the tasks were more difficult for some groups. Errors were separated into three categories, 'egocentric' (an answer from own vantage point), 'reversal' (switching left and right), and 'miscellaneous' errors (all other errors). Mean number of each error-type on left-right trials across groups were analysed (2.3.4.2.1 Figure 7). Results from one-way ANOVAs showed a significant difference across groups on all types of error; 'egocentric', $F(4, 84) = 7.45$, $p < .001$; 'reversal', $F(4, 84) = 3.67$, $p = .009$; and 'miscellaneous', $F(4, 84) = 10.02$, $p < .001$.

Further to this, one-way ANOVAs were conducted to examine whether there were differences across groups in the proportion of each error-type made (only in participants who made errors) (see 2.3.4.2.2 Table 6), showing that although the WS group were more likely to make egocentric and miscellaneous errors that 6-10 year-olds, they were less likely to make reversal errors than any TD groups.



2.3.4.2.1 Figure 7. Mean (SE) number of each type of error made on left-right trials on VPT circle task in each group. *significant difference between groups ($p < .05$), Tukey-corrected.

2.3.4.2.2 Table 6. Mean (SD) proportion of errors as each type on VPT circle across groups

	Group					ANOVA		Post-hoc[a]
	WS	5 yrs	6 yrs	8 yrs	10 yrs	F (df)	*p*	
Egocentric	42.1 (28.2)	21.2 (31.1)	16.1 (32.5)	0.0	0.0	4.63 (4, 58)	*.003*	WS > 6, 8 and 10
Reversal	31.2 (28.2)	66.1 (40.9)	78.4 (36.8)	100	100	9.79 (4, 58)	< *.001*	WS < all TD groups
Misc.	26.7 (24.1)	12.7 (26.3)	5.6 (7.0)	0.0	0.0	4.30 (4, 58)	*.004*	WS > 6, 8 and 10

[a] Tukey-corrected post-hoc tests, '>' denotes 'significantly greater than', at *.05* level

2.3.5 Object-based circle

2.3.5.1 Percentage correct.

On control trials from own vantage point (no rotation), all participants performed faultlessly, except for one participant with WS who made one error. This showed that all groups understood the task.

Responses could be divided into far trials and left-right trials. For consistency with the analysis performed on VPT circle task data, only responses to left-right trials were analysed. For left-right transformation trials, participants were asked to point a blue arrow in the correct direction of a shape that was situated either to the left or right (-90° or +90°, respectively) of the shape that the red arrow was pointing to, e.g. when the red arrow pointed to the green square, only the responses to the position of the blue circle (left) and red triangle (right) were analysed (see 2.2.5.1 Figure 4a). To examine the effect of rotation on correct responses, data were collapsed across equivalent clockwise and anti-clockwise degrees of rotation in the same way as for the VPT circle. For percentage correct across groups on the VPT circle task, see 2.3.2.1 Figure 5d.

Data were normally distributed for OB circle variables in both TD and WS groups (Kolmogorov-Smirnov, $p > .05$) and so were analysed using parametric tests. A mixed ANOVA with group as a between-participant factor (5 levels; 5, 6, 8, 10 and WS) and rotation as within-participant factor (5 levels: 0°, 45°, 90°, 135°, and 180°) was conducted. There was a significant main effect of group, $F(4, 79) = 14.92$, $p < .001$, partial $\eta^2 = .43$. Tukey-corrected post-hoc tests found 5 year-old and WS groups scored significantly more poorly than 8 and 10 year-olds ($p < .01$ for all), and 6 year-olds scored below 10 year-olds ($p = .001$). There were no other significant group differences ($p > .05$).

There was also a significant main effect of rotation, reported as a linear contrast, $F(1,79) = 137.24$, $p < .001$, partial $\eta^2 = .64$. Pairwise comparisons found a significant difference between 0° (no rotation) and all other degrees of rotation ($p < .001$ for all). There were also significant differences between 45° and 135° rotations ($p < .001$), and 90° and 135° rotations ($p < .001$).

A significant group by rotation interaction was also found, F(16, 316) = 3.17, *p*< *.001*, partial η^2 = .14, demonstrating that, similar to the pattern observed for other rotation tasks, the effect of rotation differed across groups. To further examine the effect of rotation in each group, repeated measures ANOVAs were conducted (2.3.5.1.1 Table 7). Data showed that, in contrast to all TD groups, for whom no significant detriment to performance on 180° trials was found compared to other levels of rotation, a different pattern of performance was seen in WS.

For each degree of rotation, one-way ANOVAs found a significant difference between groups for 90°, 135° and 180° rotations only (*p*< *.001* for all), with post-hoc tests revealing for 90°, 5 < 10 years (*p*< *.05*) and WS< 6, 8 and 10 years (*p*< *.05*); for 135°, 5 < 8 and 10 years (*p*< *.05*), 6 < 10 years (*p*< *.05*), and WS < 8 and 10 years (*p*< *.05*); and for 180° rotations, 5 and 6 < 10 (*p*< *.05*) and WS < 8 and 10 (*p*< *.05*).

2.3.5.1.1 Table 7. Statistical analyses of effect of rotation in each group on OB circle task

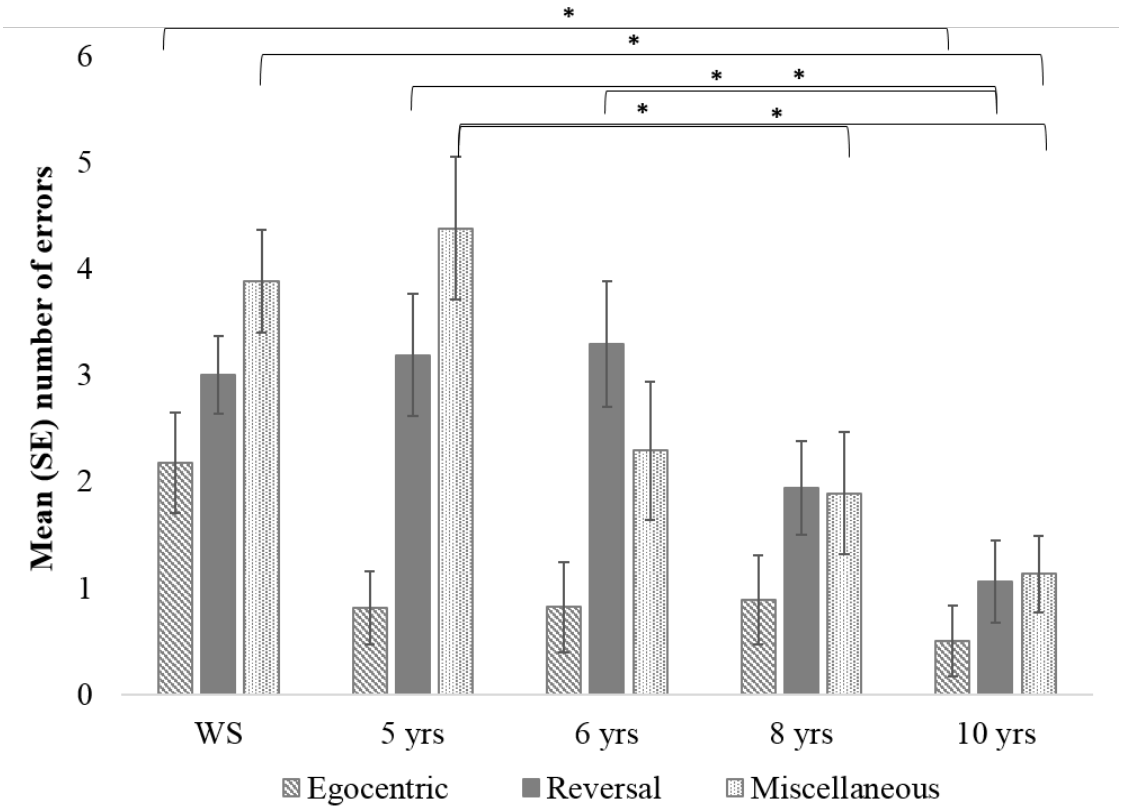
	F	*df*	*p*	Partial η^2	Post-hoc[a]
WS	104.18	(1,16)	<*.001*	.87	0°> all; 45°>135°,180°
5 yrs	42.95	(1,14)	<*.001*	.69	0°> all; 45°>135°, 90°>135°
6 yrs	33.96	(1,16)	<*.001*	.68	0°> all; 45°>135°
8 yrs	12.06	(1,17)	=*.003*	.42	0°> all
10 yrs	.48	(1,15)	=*.497*	.03	-

[a]LSD pairwise comparisons, '>' denotes 'significantly greater percentage correct', at .05 level.

2.3.5.2 Types of errors on OB circle task.

To examine errors on the OB circle task, errors were categorised into three distinct types, by the same method used in the VPT circle task. Mean number of each type of error on left-right trials was calculated from the data and one-way ANOVAs were conducted to examine the differences in Mean number of each type of error across groups (see 2.3.5.2.1 Figure 8). In line with the VPT circle, there was a significant difference in the number of each error type across groups: 'egocentric', $F(4, 83) = 2.61$, $p = .042$; 'reversal', $F(4, 83) = 3.95$, $p = .006$; and 'miscellaneous', $F(4, 83) = 5.80$, $p < .001$.

In contrast to the differences in error types in the VPT circle, one-way ANOVAs conducted to examine differences across groups in the proportion of each error-type made found no significant difference across groups in the proportion of each error-type (2.3.5.2.2 Table 8). This indicates that, unlike on the VPT circle, no group had a preponderance to make a specific type of error more than any other group on the OB circle task.



2.3.5.2.1 Figure 8. Mean (SE) number of each type of error made on left-right trials on OB circle task in each group. *significant difference between groups (p< .05), Tukey-corrected: WS > 10 yrs (egocentric and misc.); 5 and 6 years > 10 yrs (reversal); 5 years > 8 and 10 yrs (misc.).

2.3.5.2.2 Table 8. Mean (SD) proportion of errors as each type on OB circle task across groups

	Group					ANOVA	
	WS	5 years	6 years	8 years	10 years	F (df)	*p*
Egocentric	22.7 (17.8)	9.9 (18.1)	6.5 (14.4)	13.9 (22.7)	15.6 (32.5)	1.29 (4, 73)	*.284*
Reversal	33.0 (16.3)	39.2 (28.7)	59.5 (34.8)	52.3 (38.5)	40.9 (42.2)	1.64 (4, 73)	*.174*
Miscellaneous	44.3 (22.1)	50.8 (26.3)	33.9 (27.6)	33.8 (33.4)	43.3 (43.9)	<1	*.488*

2.3.6 Relationships between rotation tasks

To examine the extent to which performance on the different transformation tasks were related in TD children and WS, particularly between the two VPT tasks and between the two OB tasks, correlations were conducted on the data. *a priori* power analyses for correlations (α 0.05, effect size 0.50, 1-β at 0.8) suggest a sample size of N= 21 per group. Given the smaller group sizes in the TD groups, data were collapsed across age groups for correlational analyses. Data were normally distributed for all variables in the WS group (Kolomogorov-Smirnov, $p > .05$ for all) and for two out of four variables in the TD group (collapsed across age groups). However, for the purpose of comparability and interpretation of results, Pearsons *r* correlations were conducted both for TD and WS groups. Participant data excluded from previous mental rotation analyses were not included in the correlations.

In TD children, a significant positive relationship was found between percentage correct on the two VPT tasks (VPT path and VPT circle), r (62) = .44, $p < .001$, and a significant positive relationship between performance on the two OB tasks (monkey and OB circle), r (64) = .38, $p = .002$. In addition, performance on the VPT circle and OB circle was positively correlated in the TD group, r (65) = .56, $p < .001$, although no significant association was found between the VPT path and OB monkey task, $p > .05$.

In contrast, analyses from WS group data revealed that performance in this group was not consistent across rotation tasks, with no significant correlations between the two VPT tasks, r (19) = -.09, $p = .686$, or the two OB rotation tasks, r (19) = .42, $p = .092$; and no correlations between performances on any other mental rotation tasks ($p > .05$ *for all*).

2.3.7 Relationships between age and mental transformation

In the TD group (collapsed across groups), when controlling for BPVS scores, age was significantly correlated with performance on the VPT path, r (59) = .38, $p = .002$; VPT circle, r (59) = .32, $p = .012$; and OB circle, r (59) = .27, $p = .038$, but not

for the OB monkey task (*p> .05*). When controlling for RCPM scores, age was only correlated with performance on the two VPT tasks; VPT path, r (58) = .37, *p= .004*; VPT circle, r (58) = .28, *p= .030*.

In contrast to the pattern observed across TD children, in the WS group, performance on the OB monkey task was found to correlate significantly with chronological age, even when controlling for BPVS raw score, r (14) = .59, *p= .016*, and when controlling for RCPM, r (14) = .74, *p= .001*. Thus, older individuals with WS performed at a higher level on this monkey rotation task than younger individuals, irrespective of performance on measures of verbal and non-verbal abilities. No significant relationship was seen between chronological age and any of the other tasks in the WS group (*p> .05* for all).

2.3.8 Mental transformation and verbal and non-verbal abilities

In the TD group (collapsed across groups), when controlling for age, all mental rotation tasks except VPT path, r (57) = .22, *p = .093*, were positively correlated with RCPM scores; OB monkey, r (57) = .37, *p = .004*; VPT circle, r (57) = .40, *p= .002;* OB circle, r (57) = .39, *p = .002*. Also when controlling for age, results showed a significant relationship between BPVS raw score and OB monkey, r (57) = .29, *p= .023*.

In the WS group, a significant positive correlation was found between performance on RCPM and OB circle task scores, r (17) = .69, *p= .003*, even when controlling for age, r (14) = .66, *p= .006*. No other correlations were found between RCPM and rotation tasks for the WS group (*p> .05* for all).

Similar to TD groups, a significant positive correlation was found in the WS group between BPVS raw score and performance on the OB monkey task, r (19) = .59, *p= .007*, although this did not remain when controlling for chronological age r (16) = .38, *p = .118*. No other correlations were found between BPVS and rotation tasks (*p> .05* for all).

2.3.9. Effects of gender on mental transformation ability

To examine whether there were gender differences in mental transformation ability in TD (collapsed across groups) and WS groups separately, mixed ANOVAs with between-participant factor of gender (2 levels: male, female) and within-participant factor of task (4 levels: VPT path, OB monkey, VPT circle, OB circle), were conducted. Results from the TD groups found no significant main effect of gender, $F(1, 60) = .44$, $p = .51$. Similarly, no significant main effect of gender was found for WS groups across tasks, $F(1, 15) = .85$, $p = .37$.

2.4 Discussion

The study presented in this chapter examined object-based (OB) mental rotation and visual perspective-taking (VPT) abilities in individuals with WS compared to TD children aged 5-10 years. Developmental changes were observed in both OB and VPT abilities across the TD age-ranges presented in this study, alongside severe impairments in mental transformation abilities in individuals with WS.

2.4.1 Mental transformation abilities in typical development

In line with previous studies (e.g., Huttenlocher & Presson, 1973; Newcombe & Huttenlocher, 1992; Xistouri & Pitta-Pantazi, 2006), the results indicate a significant improvement in both OB-rotation and VPT ability between the ages of 6 and 8 years in typical development, suggestive of similar developmental progression for both abilities.

On one measure of OB mental rotation (OB monkey rotation), reaction time data yielded an effect of rotation across groups; however this was not indicative of a clear linear decline given that no significant differences were seen in rotations between 90° and 180°. This is in contrast to the linear increase in reaction time with increased degree of rotation on OB mental rotation previously identified in adults (Shepard & Cooper, 1982; Shepard & Metzler, 1971) and children (Marmor, 1975); and may be a reflection of the sensitivity of the reaction-time measure used in the current study. In

regards to percentage of correct responses however, performance *was* seen to decline with greater levels of imagined transformation in 5 and 6 year-olds. This was not seen in 8 and10 year-olds, who showed near-ceiling performance on this task. A similar pattern was observed in the OB circle task, with no effect of rotation seen above 45° in 8 year-olds and no effect of rotation in 10 year-olds, due to consistently good performance across the task in older children. These findings therefore provide a clear picture of changes in mental rotation performance with age in typical development.

In contrast to OB mental rotation, a decline in performance with rotation on VPT tasks is often not reported in typical adults (e.g. Wraga et al., 2000; Zacks et al., 2000). However, such a decline has been identified in TD children (Roberts & Aman, 1993). Although Roberts and Aman (1993) examined reaction times, the present study demonstrates that a decline in performance with increased imagined rotation can also be observed in relation to accuracy on VPT tasks. On the two VPT tasks, TD children under 8 years exhibited difficulties in determining left-right body coordinates (despite having eliminated any requirement to understand the terms 'left' and 'right') with increased misalignment from actual viewpoint. In contrast, 10 year-olds (on the VPT path) and 8 and 10 year-olds (on VPT circle) showed no difference in accuracy between 90° and 180° rotations, a pattern similar to that observed in typical adults. This contributes to the literature in TD children, indicating that between 8 and 10 years of age, children may develop a more appropriate strategy for performing imagined transformations of the self to different locations, to be more in-line with strategies observed in typical adults (Wraga et al., 2000; Zacks et al., 2000).

2.4.2 Mental transformation abilities in Williams syndrome

The results from the WS group data in this study were also in line with that of previous findings of poor mental rotation abilities in this group (Farran & Jarrold, 2004; Farran et al., 2001; Vicari et al., 2006). In particular, when required to imagine the rotation of a single image (OB monkey rotation), despite demonstrating an understanding of the task on trials in the upright position, as a group, participants with

WS scored significantly below all TD groups, and performed at chance level on all degrees of rotation. Given that performance in the WS group was significantly below all TD groups even on 0° trials, this suggests that difficulties in visual matching in WS may have contributed somewhat to these results. However, an effect of rotation was still identified in the WS group, suggesting that, similar to the pattern observed in TD 5 and 6 year-olds, some individuals with WS found the task increasingly more difficult with escalating degrees of rotation, i.e., they were able to use mental rotation. This is likely a reflection of higher levels of performance on this task with chronological age in WS participants, a finding discussed in more detail later. Further to this, RT data demonstrated significantly slower response times in WS compared to TD 8 and 10 year-olds, although this pattern may reflect slower motor abilities related to pressing the response buttons in WS rather than speed of mental rotation.

This study also provided insight into VPT abilities in WS compared to TD 5-10 year-olds. Two VPT tasks were conducted to examine the ability to perform imagined movement of the self around a circular array and the ability to determine left-right body coordinates following imagined self-rotations to either 90° or 180° from actual viewpoint. Participants with WS performed poorly on both VPT tasks, indicative of profound difficulties at all angles of imagined self-rotation, with performance at chance on rotations above 90° on the VPT circle task. This is in line with previous research that indicated chance performance in WS when asked to imagine the perspective of another individual at 180° from own viewpoint (Farran et al., 2010). The current results extend these findings, demonstrating difficulties in this group at even lesser degrees of imagined self-rotation. On the VPT path task, scores in the WS group were not significantly different to that of TD 5 year-olds, albeit at a level above chance on trials requiring imagined rotation of the self by 90°. One consideration is that it may have been possible to solve 90° trials by turning the head to look either to the left or right. This may explain above chance performance on these trials across groups. This is supported by the results of the VPT circle task. Here, given the extent of imagined self-movement required for rotations greater than 45°, turning of the head may have only

supported performance on 45° trials. The results reflect this, with WS individuals scoring at chance level on trials 90° and above, and scoring below 6, 8, and 10 year-olds.

At imagined self-rotations of 180° on the VPT path task, both TD 5 year-olds and participants with WS yielded scores significantly below chance, indicating that not only do young TD children and individuals with WS have profound difficulties in imagining turning the self by 180°, they demonstrated a similar preponderance to select an egocentric option (choosing the left or right that corresponded to their actual viewpoint). Similarly, when asked to imagine the rotation of the self around an array of objects (VPT circle), performance in the WS group fell to chance level on trials that required imagined rotations greater than 45°, indicative of profound difficulties with such activities.

2.4.3 Different patterns of performance in TD and WS groups

The level of performance in individuals with WS both on OB and VPT tasks was in line with that of TD children of comparable non-verbal ability. Although WS participants were no different from 8 and 10 year-olds on the test of verbal ability, they performed at the level of 5 and 6 year-olds on non-verbal cognition as measured by RCPM. This pattern of poor non-verbal abilities in contrast with relatively good verbal skills is a typical finding for individuals with WS (Jarrold, Baddeley, Hewes, & Phillips, 2001; Martens et al., 2008). At first glance, performance on the transformation tasks in WS is therefore unsurprising, given that individuals with WS have often been found to perform at a similar level to TD children aged 4-6 years on a number of cognitive tasks including spatial (Nardini et al., 2008) and numerical abilities (Ansari, Donlan, & Karmiloff-Smith, 2007). However, in the current study, despite a similar level of performance in the WS group as 5 and 6 year-olds on most tasks, individuals with WS demonstrated an atypical pattern of performance.

The observed pattern of performance in WS on OB and VPT tasks in this study may, therefore, reflect that of a divergent developmental trajectory rather than what could be simply accounted for by developmental delay. This was reflected in part by

the types of errors made on the VPT circle task compared to TD groups. On the VPT circle task, egocentric errors were the most prominent error type in individuals with WS, compared to left-right reversal errors making up the majority of errors in TD children. This prominence was not identified in the OB circle task, suggesting that imagined rotations of the self may present additional egocentric difficulties in WS that are not seen with imagined rotations of objects in a similar array.

Mental rotation difficulties in WS have previously been attributed to deficits in the perceptual processing of spatial orientation (Farran & Jarrold, 2004), and are indicative of fractionated dorsal stream functions in this disorder. Performance on OB rotations and VPT tasks likely recruit similar underlying neural mechanisms (Kosslyn et al., 1998; Lambrey et al., 2012; Wraga et al., 2005; Zacks et al., 2000; Zacks et al., 2002; Zacks et al., 1999). As such, difficulties encoding an allocentric frame of reference for successful OB rotations may go hand in hand with difficulties in VPT, where an individual is required to consistently update their egocentric location within an allocentric reference frame. Updating the location of the self during imagined rotations is thought to rely on the successful translation between egocentric parietal representations and allocentric hippocampal spatial codes (Burgess, 2008; Lambrey et al., 2012; Vann et al., 2009). Accordingly, given that a number of additional cortical regions are involved in VPT tasks to those in OB rotations, deficits in dorsal stream functioning may be insufficient to explain the specific difficulties evident in both types of task. The profound difficulty in updating one's egocentric location on the VPT task in WS is therefore consistent with atypical processing in anterior hippocampal (Meyer-Lindenberg et al., 2005) and parietal-occipital regions (Boddaert et al., 2006) in this group. In addition, difficulties in updating the imagined location of the self may explain why individuals with WS were more likely to make egocentric than left-right reversal errors (as seen in TD children), in the current study.

The large proportion of egocentric errors in WS is similar to findings that indicate young children interpret VPT instructions egocentrically and have difficulty in rotating this frame of reference in order to complete these tasks (Epley et al., 2004).

Epley and colleagues also suggested that adults initially interpret instructions egocentrically, but have a superior ability to inhibit an egocentric response and adjust to using an appropriate strategy quickly and effectively. Difficulties in inhibition have been reported in individuals with WS (Menghini, Addona, Costanzo, & Vicari, 2010), and as such, failures in self-rotation in WS may also reflect difficulties in suppressing an egocentric response.

On the OB circle task, only the WS group demonstrated performance on 180° that was significantly below any other rotation trial. This may have, like in the VPT circle task, reflected a different pattern of performance than seen in typical development. For instance, whereas some TD children may have been able to use an alternative strategy to support performance on 180° trials such as a verbal or 'flipping' strategy, individuals with WS did not demonstrate the ability to do so.

2.4.4 Individual differences in WS

A large amount of variability was observed in the performance of the WS group within each transformation task. This may have reflected the ability of some individuals with WS to consistently mentally rotate both objects and themselves at a level similar to older typically developing children. However, in the WS group no relationship was found between the 4 rotation tasks, suggesting large variability and an inconsistent pattern of performance in this group that may have been more attributable to noise. This was in contrast to the TD group, who – as with earlier research in adults (Hegarty & Waller, 2004)- demonstrated relatively consistent levels of attainment across the majority of VPT and OB tasks, indicative of similar mechanisms underlying both self- and object-based rotations in typical development. Despite this, a relationship was not identified between TD scores on the VPT path and monkey task, suggesting that an ability to rotate a single object may not be related to the ability to imagine one's self turning within a path.

Further examination into individual differences in performance on these tasks in WS found that OB rotation abilities as measured on the monkey task increased with

chronological age, even when controlling for verbal or non-verbal abilities. This is contrasted with our findings in TD children, for whom OB mental rotation of a single image was positively related to verbal ability. Thus, TD children who were able to apply verbal strategies during these tasks may have further supported their performance on the monkey task.

In line with our findings of age in WS and OB mental rotation, in a study examining development trajectories of spatial reference frames in WS, Nardini et al. (2008) found that older WS participants aged 26-42 were the only WS group in their study to score above chance on a task requiring the ability to use an array-based spatial frame of reference (i.e. OB mental rotation). Although this difference in ability between younger and older WS individuals remained marginal, this finding, alongside the present results, indicates that some older individuals with WS may have developed strategies to successfully complete OB rotation tasks that are independent of verbal or non-verbal development. However this was only shown (in the present study) on a task involving the mental manipulation of a single object and no such relationship was evident between WS age and mental manipulation of multiple items in an array (OB circle). It could be inferred from this that difficulties resulting from having an additional cognitive load of more than one object to mentally transform do not remediate with age in this group and is more associated with level of non-verbal cognition, as shown in the relationship between RCPM performance and OB array rotation. In the WS group, age-related factors such as experience with tasks or games requiring mental rotation may have facilitated performance, as seen in TD adolescents (Okagaki & Frensch, 1994). To address limitations of the current study, future research should therefore include, not only a greater age-range of individuals with WS, but also examine age-related differences in spatial performance, and assessments of experience with mental rotation tasks. In addition, the use of tasks that examine performance across comparable degrees of rotation would allow clearer comparison of performance across different tasks in individuals with WS.

2.4.5 Small- and large-scale tasks

The ability to update self-to-object representations is important for successful large-scale spatial navigation, and performance on such environmental learning tasks has been found to be associated with the ability to imagine one's self rotating at a small scale (Kozhevnikov et al., 2006). The profound deficits on small-scale VPT tasks in WS therefore suggest that such strategies may not be available to support performance on navigational activities in the same way as TD children and adults.

2.5 Conclusions

In sum, significant improvements in visuospatial tasks that involve mental transformation of objects or the self are seen between 6 and 8 years of age in typically developing children. Moreover, near ceiling performance was seen by 10 years of age on the majority of tasks, indicating substantial maturity of these abilities by this age. In contrast, extensive difficulties in performing mental transformations both of objects and the self were identified in individuals with WS. As a group, participants with WS performed in line with what could be expected based on non-verbal ability, often demonstrating performance at a level similar to TD 5 and 6 year-olds. However, a different pattern of errors was observed in the WS group compared to TD children, indicative of divergent rather than simply arrested or delayed development. When asked to imagine the rotation of a single image, performance in WS was positively correlated with chronological age, suggesting that some older individuals with WS may have developed successful techniques by which to mentally rotate objects.

Findings in part suggest that poor performance on VPT in WS is related to difficulties in inhibiting a prepotent egocentric response. However, it is likely that deficits in imagined rotations of the self are related to atypical processing in cortical regions associated with the translation of egocentric and allocentric spatial frames of reference required for successful updating of the position of the self, following both imagined and actual movement. Severe impairments in mental transformation abilities in WS are likely to be implicated in performance in large-scale spatial tasks, particularly

given the known associations in typical adults between VPT and navigation performance (e.g., Kozhevnikov et al., 2006). This is examined further in chapter 4.

Chapter 3

Study 2: Egocentric and allocentric navigation strategies in typical development and Williams syndrome

3.1 Introduction

The study of small-scale visuospatial cognition in individuals with Williams syndrome (WS) presented in study 1, offered preliminary insight into the specific deficits in the use of different spatial frames of reference associated with this disorder. Study 2 presented in the current chapter aimed to examine the manner in which such deficits are evident in large-scale space, particularly in navigational learning in WS, compared to performance in typically developing (TD) children aged between 5 and 10 years.

In large-scale space, the use of an egocentric spatial frame of reference (the encoding of environmental locations in relation to one's own body), allows an individual to accurately retrace a route from one location to another, using simple stimulus-response navigation (Burgess, Jeffery, & O'Keefe, 1999). However, being able to use an allocentric spatial reference frame, that is, encoding the spatial relationships between landmarks (O'Keefe & Nadel, 1978), facilitates more complex navigation, such as the ability to make short-cuts or to understand how to relocate oneself when starting from a novel location in a familiar environment.

In typical development, when spontaneously navigating through an environment, both children and adults predominantly rely on the use of a *sequential* egocentric strategy, by recalling the temporal order of body turns at specific (and spatially distinct) environmental locations (Bullens, Iglói, et al., 2010; Iglói et al., 2009). Using a virtual navigation task, Bullens and colleagues found that the ability to successfully employ an allocentric strategy to navigate develops progressively between 5 and 10 years of age, but is systematically utilised only when the task demands a more complex understanding of the spatial relationships in the environment. This is in line with research that suggests a developmental change between 6 and 8 years of age from a

reliance on viewpoint-dependent spatial processing (e.g., the use of stored views of spatial locations in relation to the self), to more flexible viewpoint-independent processing, or environment-centred spatial representations that allow accurate recall irrespective of the viewer's movements (Nardini et al., 2009).

Using a spatial coding paradigm to examine the development of body-, environment- and object-based spatial frames of reference in WS, Nardini et al. (2008) found that individuals with WS exhibit specific difficulties on tasks requiring the encoding of spatial relationships between landmarks in a small-scale array. This is indicative of particular difficulties in WS in the use of an intrinsic (array-based) frame of reference. Further to this, in a series of small-scale visual spatial judgement tasks, individuals with WS were found to have impairments in the use of both egocentric and allocentric frames of reference (Bernardino, Mouga, Castelo-Branco, & van Asselen, 2013), suggesting that impairments in coding spatial information in WS are not just a result of deficits in memory capabilities, but that impairments also occur at the perceptual level.

Difficulties in WS with encoding spatial locations of objects in relation to the self and other objects were similarly presented in study 1 using tasks requiring imagined rotations of the self and objects. These findings are in line with previous reports of mental transformation difficulties in this disorder (Farran et al., 2001; Stinton et al., 2008). Imagined rotations of the self (visual perspective-taking, VPT), in particular, require the ability to update egocentric spatial locations within an allocentric frame of reference, and this ability is thought to be supported by hippocampal and medial temporal lobe structures (Burgess, 2008; Lambrey et al., 2012; Vann et al., 2009). Known structural and functional abnormalities of the hippocampus in WS (Meyer-Lindenberg et al., 2005) are therefore likely to be associated with difficulties observed in WS on tasks that require this kind of imagined rotation. In addition, given the known deficits in dorsal stream functioning in WS (J. Atkinson et al., 2003; J. Atkinson et al., 1997), difficulties in egocentric spatial coding supported by the dorsal stream in typical

adults (Milner & Goodale, 1995; Packard & Knowlton, 2002), may also contribute to such deficits on imagined rotation tasks in these individuals.

In typical adults, increased activition in the hippocampal region is associated both with allocentric spatial coding (understanding the relationships between objects in an array), and with large-scale allocentric navigation (Burgess et al., 1999; Burgess et al., 2002). It can be inferred therefore that individuals with WS are also likely to present with difficulties on large-scale tasks that require the use of allocentric spatial coding. Moreover, in typical adults, the ability to imagine the self rotating predicts performance on navigation tasks that require the individual to constantly update self-to-object and object-object locations when moving through an environment, namely the ability to utilise allocentric coding (Kozhevnikov et al., 2006). Thus, difficulties on small-scale tasks in WS suggest that large-scale spatial tasks, particularly those requiring allocentric encoding, are likely to be problematic for this group.

Previous studies examining large-scale environmental learning have shown that not all large-scale spatial abilities are equally impaired in WS. For instance, individuals with WS can successfully learn to navigate and accurately retrace their route both in real-world (Farran et al., 2010) and virtual environments (Farran, Courbois, Van Herwegen, & Blades, 2012). However, in line with small-scale relational coding difficulties, in the 2010 study, Farran and colleagues found that in a real-world task, individuals with WS showed deficits on tasks requiring an understanding of spatial relationships in the environment. That is, when asked to point to the location of imperceptible landmarks from positions along a route, individuals with WS displayed a high number of errors compared to TD children, consistent with the predicted difficulties in allocentric encoding in WS.

Of note, real-world navigation tasks may pose a particular difficulty for individuals with WS in relation to the physical demands of the task and therefore the extent to which participants are able to gain extensive experience in an environment. In typical adults and children, extended experience within an environment leads to enhanced understanding of the spatial relationships between landmarks (Anooshian &

Young, 1981; Golledge & Spector, 1978; Lehnung et al., 2003; Siegel & White, 1975). Reduced opportunities for independent navigation and active exploration in real-world environments has been implicated in poor spatial-relational knowledge in individuals with physical disabilities (Foreman, 2007; Foreman et al., 2003; Stanton, Foreman, & Wilson, 1998). This may also be the case for individuals with learning difficulties (Mengue-Topio, Courbois, Farran, & Sockeel, 2010). Given the time restraints and physical demands involved in navigating a route multiple times, real-world tasks in WS may be limited by the scope of experience that each participant can gain from an environment. This suggests that difficulties in spatial relational knowledge identified in WS on previous real-world tasks (e.g. Farran et al., 2010) is, in part, a consequence of this lack of environmental experience, and that further experience in these environments may have led to the development of more complex spatial representations. As such, it is not clear whether increased exposure to an environment in individuals with WS would improve the ability to encode spatial relationships in that setting and apply an allocentric spatial frame of reference when the task demands.

Using a radial-arm maze, Mandolesi et al. (2009) examined the mnesic components related to large-scale visuospatial difficulties in WS. The results showed that individuals with WS were impaired in acquiring procedural competencies and spatial working memory. This is in line with other findings implicating the role of a deficit in dorsal stream functioning on poor spatial working memory in WS (O'Hearn, Courtney, Street, & Landau, 2009). Mandolesi and colleagues found that perseverative errors in exploration were also evident in some participants with WS, a further reflection of spatial memory and planning difficulties in this group. Others have also identified similar perseverative errors in WS during navigation (Farran et al., 2012). Such difficulties in spatial working memory and use of inefficient exploration strategies in WS may underlie some of the difficulties demonstrated on tasks requiring the recall of landmark locations (e.g., Farran et al., 2010). Importantly, Mandolesi and colleagues found that some individuals with WS demonstrated an understanding of the spatial representation of the test layout when asked to draw the environment; the only indication in the literature of possible spatial relational knowledge in WS. In another

real-world study however, search strategies in WS were found to be disorganised and ineffective compared to TD children, and individuals with WS failed to develop an understanding of the environmental layout (Foti et al., 2011).

Our understanding of whether individuals with WS are able to develop spatial relational knowledge and utilise an allocentric spatial frame of reference in large-scale space, therefore, remains ambiguous. Although individuals with WS have demonstrated successful route-learning abilities, to date no study has specifically examined the navigational strategies employed in this group, and in particular the use of egocentric and allocentric spatial frames of reference. The aim of the present study was to examine navigational strategies in WS in a large-scale virtual environment (VE), compared to TD children between 5 and 10 years of age. Using a virtual cross-maze design, spontaneously employed navigational strategies were examined across groups, together with the ability to make use of allocentric spatial coding when required.

Given the potential of exploring a VE multiple times within a relatively short time period and without the physical demands of real-world environments, the use of VEs to examine large-scale spatial difficulties may be a useful resource in WS. For a further discussion regarding the use of VEs to examine spatial navigation, see 1.6.

Allocentric spatial strategies are thought to be supported in part by the hippocampal region (Iaria et al., 2007; King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002; McNamara & Shelton, 2003; O'Keefe & Nadel, 1978), particularly the right hippocampus (Iglói et al., 2010). Given the known hippocampal impairments in WS (Meyer-Lindenberg et al., 2005), difficulties in the use of an allocentric strategy in WS were anticipated in the current study. Sequential egocentric spatial representations, in contrast, are related to left hippocampal (Iglói et al., 2010) and dorsal stream activation (Milner & Goodale, 1995), a finding supported by neuroimaging during the use of egocentric navigation strategies (Committeri et al., 2004; Galati et al., 2000; Neggers, Van der Lubbe, Ramsey, & Postma, 2006). Deficits in dorsal stream functioning have been identified in individuals with WS (e.g., J. Atkinson et al., 2003; J. Atkinson et al., 1997; Nakamura, Kaneoke, Watanabe, & Kakigi, 2002). As such,

despite previous findings of successful performance on route learning tasks in WS (e.g. Farran et al., 2010), it was hypothesised that, where TD children may predominantly employ a sequential egocentric strategy, individuals with WS may demonstrate alternative navigation strategies on such tasks, suggestive of an atypical pattern of coding spatial frames of reference in large-scale environments.

3.2 Methods

3.2.1 Participants

The same sixty-seven typically developing (TD) children who were recruited and completed tasks in study 1 were also included in the present study. As before, TD participants were separated into four age groups; 5, 6, 8, and 10 year-olds. The same twenty individuals with Williams Syndrome (WS) who successfully completed the mental transformation tasks in study 1 were also included. All WS participants had received a positive diagnosis of WS, based on a "fluorescence *in-situ* hybridisation" (FISH) test for deleted Elastin gene on the long arm of chromosome 7, as well as phenotypic diagnosis from a clinician.

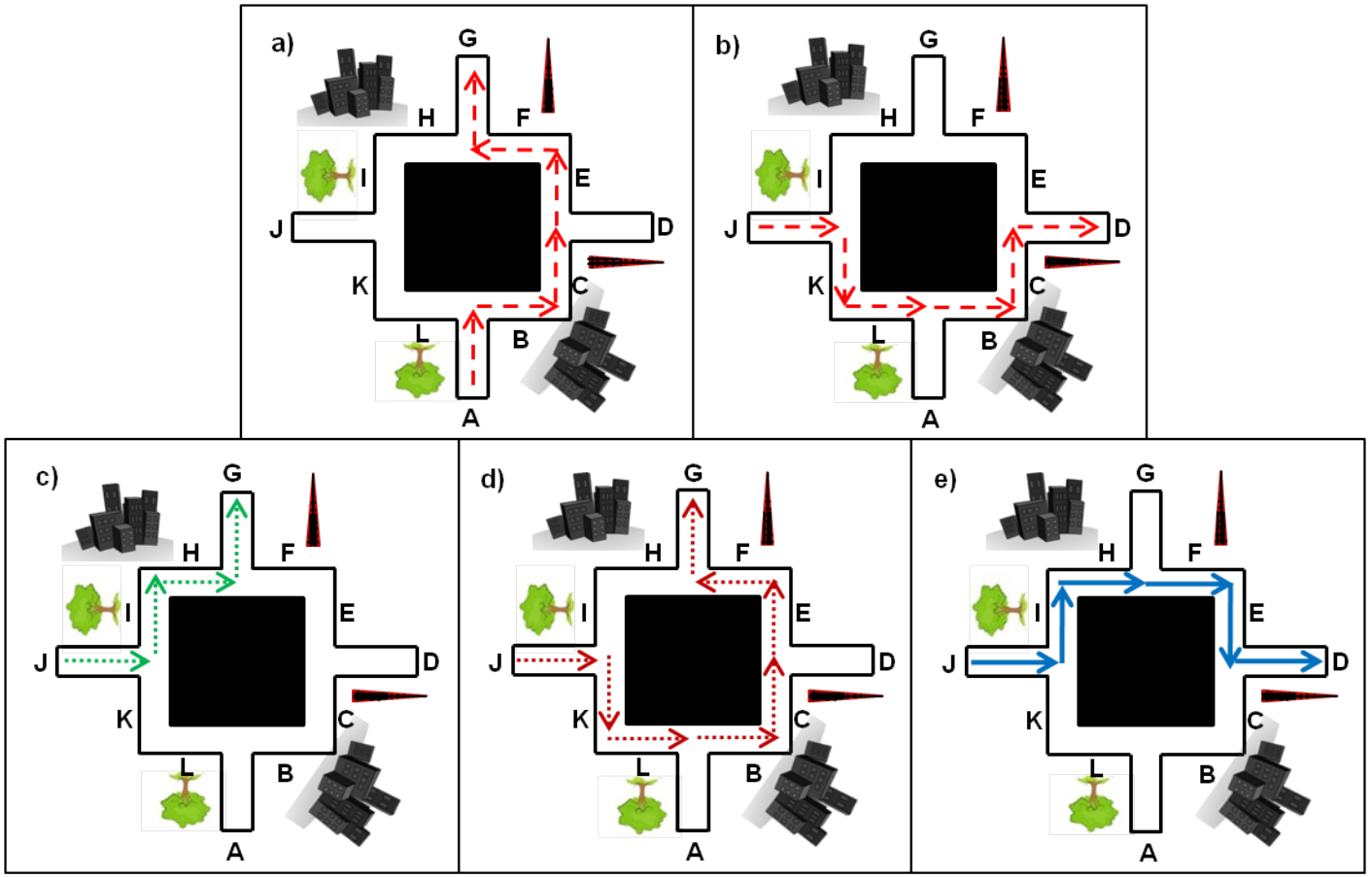
Nine participants from the original TD group (N=6, 5 year-olds; N=2, 6 year-olds; and N=1, 8 year-old) and three from the original WS group did not manage to complete the VE tasks in the present study successfully, due to lack of motivation or concentration. Data for these participants were excluded from subsequent analyses. Six more TD 5 year-olds were therefore recruited to maintain comparable group sizes, all of whom completed the tasks successfully. Therefore, data were analysed from 64 TD children; 5 year-olds (N=16, 10 males, Mean age (years; months) = 5;07, SD = 0;04, CA range = 5;01 – 6;01); 6 year-olds (N=15, 10 males, M_{age} = 6;08 years, SD = 0;03, CA range = 6;04 – 7;05); 8 year-olds (N=17, 10 males, M_{age}= 8;03, SD = 0;04, CA range = 7;07 – 8;08); and 10 year-olds (N=16, 9 males, M_{age} =10;01, SD = 0;03, CA range = 9;06 – 10;09), and 17 participants with WS (9 males, M_{age}= 21;10, SD = 8;05, CA range = 13;01 – 43;03). Verbal and Non-verbal abilities were assessed using the

British Picture Vocabulary Scale-III (BPVS-III; Dunn et al., 2009) and the Ravens Coloured Progressive Matrices (RCPM; Raven et al., 2003), respectively.

3.2.2 Virtual environment (VE)

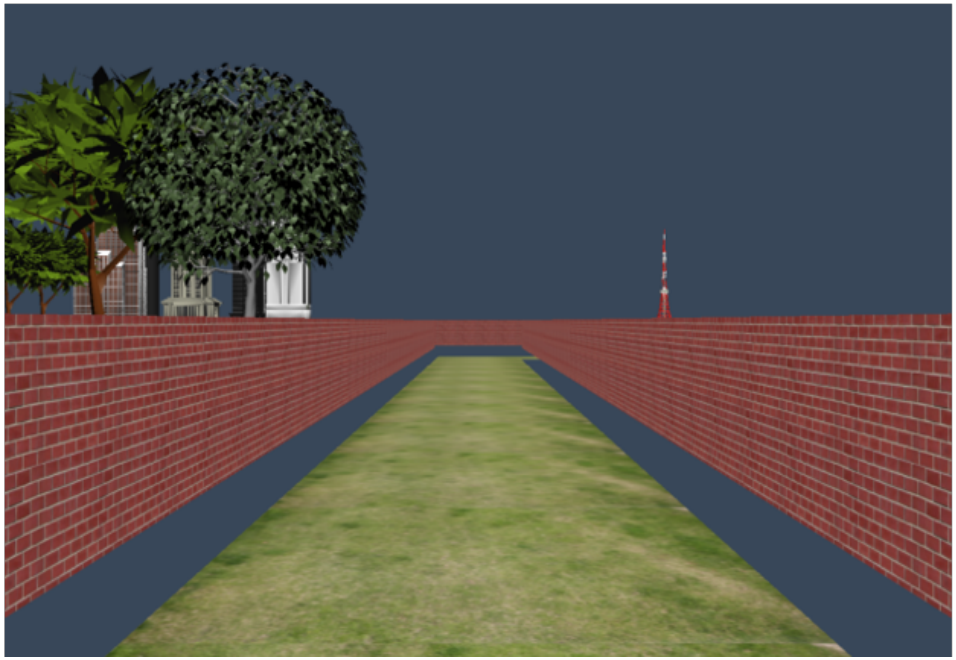
The interactive VE cross-maze was developed using The Vizard Development Edition software (www.worldviz.com), and presented on a 17" laptop screen on a table-top in front of the participant. Adapted from a five-arm maze used in other studies (e.g. Bullens, Iglói, et al., 2010; Iglói et al., 2009), the VE cross-maze task presented participants with a more simple environmental layout within which individuals were able to use either a 'sequential egocentric' or 'allocentric' spatial strategy to navigate, or a combination of the two (a 'mixed' strategy). For a birds-eye schematic image of the cross-maze layout, see 3.2.2.1 Figure 9.

The VE consisted of four paths (A, D, G, and J) extending from a central square. The central square was made up of eight paths, made distinct by a turn or a junction (B, C, E, F, H, I, K and L). The alleys of the central square and the extending pathways all had red brick walls and therefore appeared identical from any starting position and all paths between decision points were the same length. Surrounding the environment were six distal landmarks, consisting of three different landmarks appearing twice each (two trees, two city landscapes and two red towers). Each distal landmark appeared twice around the environment so that participants would have to encode landmarks in terms of their relationship to each other and the paths, and not use them as directional cues. Participants navigated through the environment using the keyboard arrow-keys. Selected views from within the VE, as seen by the participant, are displayed in 3.2.2.2 Figure 10.

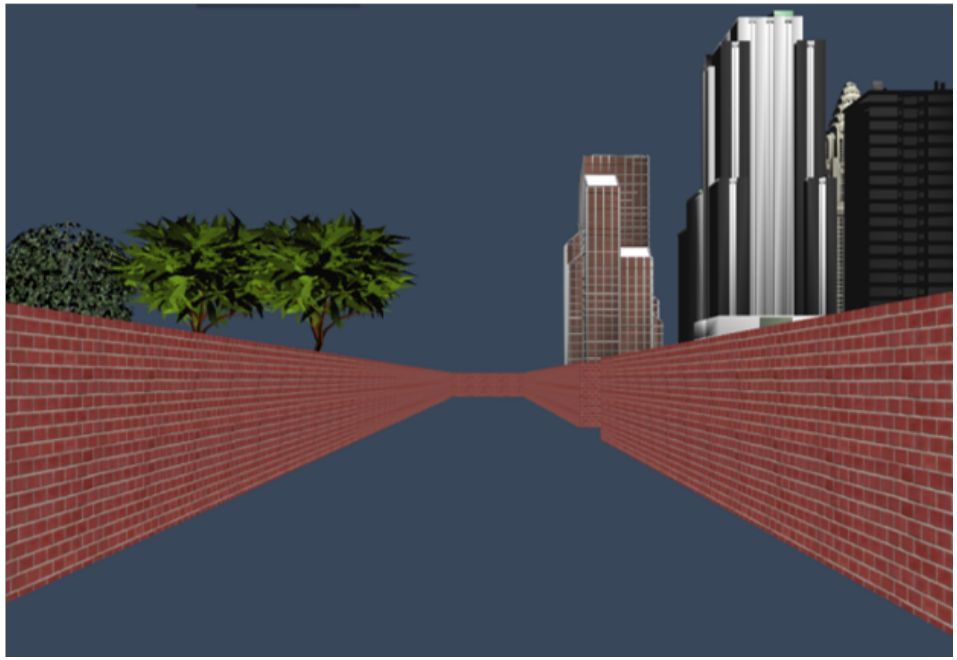


3.2.2.1 Figure 9. Schematic layout of cross-maze with routes taken by participants using different strategies: a) route taken during learning and eight normal test trials, b) route taken using a Sequential Egocentric strategy, c) Allocentric, d) Mixed, e) Mirrored Egocentric.

a)



b)



3.2.2.2 Figure 10. Screen shots from the virtual environment (VE); a) view from beginning of path 'A', showing the grass path for the learning trial; b) view from path 'F' towards path 'H' and junction of path 'G' (right).

3.2.3 Design and procedure

3.2.3.1 Learning phase.

Participants were asked to navigate from the starting position at the beginning of path A to find a "hidden exit" at the end of path G. Participants were unable to see the end of any other pathway from any starting position within the environment. During the learning phase, participants were first shown the optimal route to the hidden exit by following a grass path (see 3.2.2.2 Figure 10a). Once the target location was found, a "Yippee!" reward sound was played and the programme window closed. The participant was then returned to the starting position in path A, without a grass path, for the first learning trial. Here, participants were required to walk the route from memory. During the learning trials (maximum 10 trials), participants had to navigate down the correct path to reach the hidden target without error on two trials to move on to the testing phase. During learning trials, invisible walls were positioned one quarter of the way down incorrect paths to guide learning. Participants were therefore able to look down the incorrect turns but not travel down them further than this point. If participants incorrectly navigated to the point of hitting an invisible wall, this was counted as an error.

3.2.3.2 Testing spontaneous navigation strategies.

Following successful learning (reaching criterion of two correct learning trials), participants were told that the invisible walls had now been removed and so could travel down any path they wanted. Participants were instructed that for each test trial, they must try to reach the same hidden exit (in path G) by the shortest route possible. Participants then completed twelve test trials.

To intermittently test the strategy that the participant was using, the twelve test trials were interspersed with four 'strategy test' trials (trials 3, 7, 9, and 12); where instead of the normal starting point in path A, the participant was unsuspectingly placed at the beginning of path J as a starting location. From both starting positions (J and A),

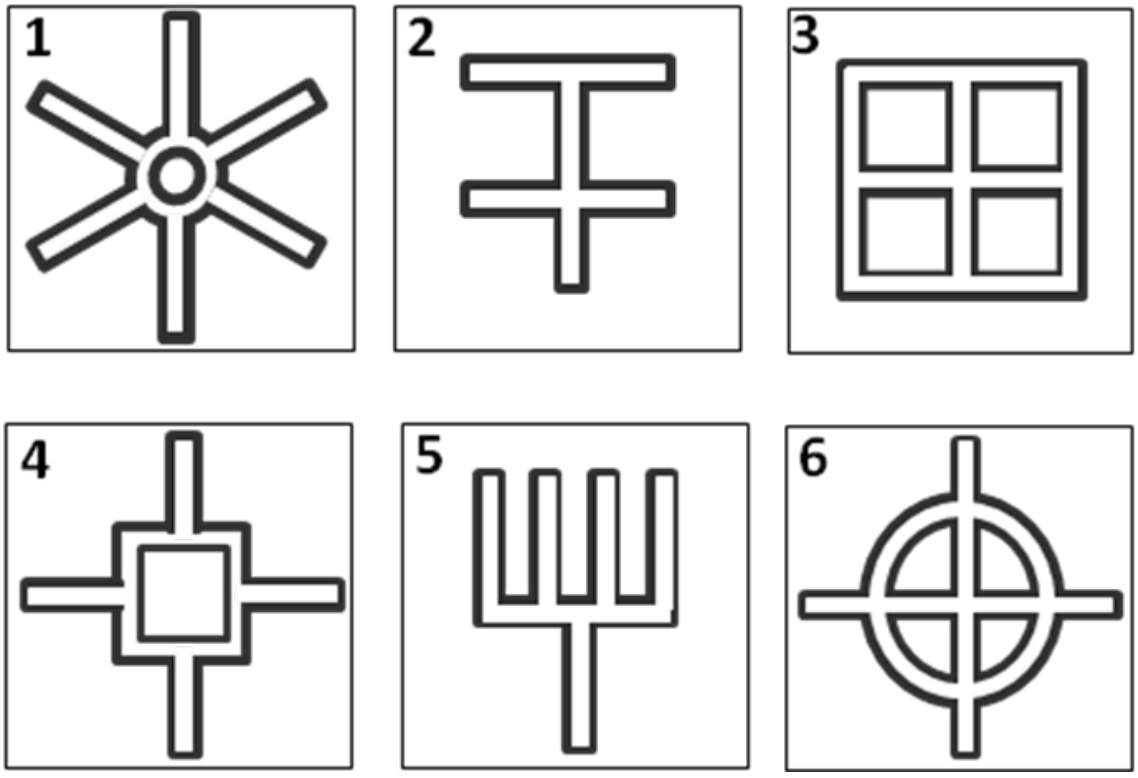
the views contained similar distant landmarks, including a tree, cityscape and red tower. Therefore, participants who spontaneously relied on the use of a 'sequential egocentric' strategy may not have encoded the spatial layout, even if they could identify similar landmarks, and would have followed the same sequence of body turns as usual (3.2.2.1 Figure 9b). Participants spontaneously using an 'allocentric strategy', however, would have identified the different spatial relationships between landmarks surrounding the environment and navigated directly to the correct exit by the shortest route (3.2.2.1 Figure 9c). On the four spontaneous strategy tests, both the ends of paths G and D revealed the reward sound as positive feedback for the use of either of these spontaneous strategies. Therefore, participants who used an egocentric strategy would not be alerted to the change in starting position, and they would continue to use their spontaneous strategy on subsequent test trials.

3.2.3.3 Enforced allocentric strategy trials.

To examine whether participants were able to navigate using an allocentric strategy when required, they were asked to navigate in the same VE to a new hidden exit from different starting points. Participants were first told that the hidden exit had moved to a new place. They were then placed in path J and asked to follow the grass path to the hidden exit now in path A. Participants then completed the learning trials without the grass until they had successfully navigated to the new hidden exit on two trials, i.e. they had reached the learning criterion. Following learning, participants were informed that they would now have to find this hidden exit from different starting positions and were encouraged to take note of the environmental landmarks to remind them of the location of the hidden exit. Participants completed six test trials from different starting positions (three from path G and three from path D, presented in a random order). The reward sound was played only at the end of path A, following the use of an allocentric strategy.

3.2.3.4 Layout knowledge test.

Following the enforced allocentric strategy trials, to further examine whether participants had developed an allocentric understanding of the environmental layout, participants were asked to choose the correct layout of the environment from a set of six map options (3.2.3.4.1 Figure 11). Correct selection of an environment layout, or ability to draw a 'map' of the environment is considered to be a valid measure of large-scale allocentric knowledge (Billinghurst & Weghorst, 1995; Morganti, Carassa, & Geminiani, 2007).



3.2.3.4.1 Figure 11. Layout knowledge test: six environment layout choices

3.3 Results

3.3.1 Verbal and non-verbal abilities

To examine the difference across groups on BPVS and RCPM scores, one-way analyses of variance (ANOVA) were conducted for each, with group (5 levels; 5y, 6y, 8y, 10y, and WS) as a between-subjects factor (see 3.3.1.1 Table 9). This demonstrated

an uneven cognitive profile in WS, characteristic of the disorder (Bellugi et al., 2000; Jarrold et al., 1998), with nonverbal abilities at a level no different from TD 5 year-olds, and relatively higher verbal abilities, significantly greater than TD 5 and 6 year-olds, at the level of TD 8 and 10 year-olds.

3.3.1.1 Table 9. Mean (SD) participant scores on BPVS-III and RCPM.

	Group					ANOVA		Post-hoc[a]
	WS (N=17)	5 years (N=16)	6 years (N=15)	8 years (N=17)	10 years (N=16)	F (df)	*p*	
BPVS raw[b]	123.65 (22.38)	78.94 (13.49)	91.33 (14.25)	112.35 (15.78)	130.81 (15.18)	27.55 (4, 80)	< *.001*	5 = 6 < 8, 10 and WS 8 < 10 WS = 8 and 10
BPVS standard[c]	-	97.31 (10.43)	95.13 (10.97)	102.47 (14.96)	97.44 (12.92)	1.01 (3, 63)	.396	-
RCPM[d]	16.82 (3.15)	18.63 (3.85)	23.67 (5.07)	27.94 (5.25)	30.56 (3.37)	31.96 (4, 80)	< *.001*	5 < 6, 8, and 10 6 < 10 WS < 6, 8 and 10

[a] Tukey-corrected post-hoc tests, '=' refers to no significant difference at .05 level, and '<' denotes $p < .01$; [b]BPVS-III: British Picture Vocabulary Scale-III raw scores; [c]BPVS-III standardised scores; [d]RCPM: Ravens Coloured Progressive Matrices (RCPM) raw scores

3.3.2 Learning trials

Following the original learning trial with the grass path, the number of trials (including two correct criterion trials) taken to successfully reach criterion (required to advance to the testing phase) was examined in each group.

Results of a one-way ANOVA showed a significant effect of age on mean number of trials taken to learn the route to the hidden target, F (4, 80) = 4.59, *p= .002*. Tukey-corrected post-hoc tests showed that TD 10 year-olds (M= 2.75, SD= .68) required significantly fewer trials to learn the route than the 5 year-old (M= 4.38, SD= 1.71, *p= .033)*, 6 year-old (M= 4.67, SD= 1.88, *p= .009)* and WS (M= 4.76, SD= 2.08, *p= .003)* groups, but not 8 year-olds (M= 3.76, SD= .97). No significant difference in number of trials was found across any other groups (*p> .05,* for all).

3.3.3 Test trials

To examine whether performance on the eight trials in the test phase – not including the four spontaneous strategy trials – was successful for each participant, the percentage of trials without error (direct route taken to the exit, without traversing more than half way down incorrect paths) was calculated for each group.

Results of a one-way ANOVA showed steady performance on the eight test-phase trials following learning in each group, with no significant difference in percentage of correct test trials found across groups: 5 years (Mean = 77.34%, SD= 20.01%); 6 years (Mean = 71.67%, SD= 26.50%); 8 years (Mean = 71.32%, SD= 21.99%); 10 years (Mean = 80.47%, SD= 21.39%); WS (Mean = 72.22, SD=19.91%), F(4, 81) = .56, *p = .691*. This shows that after reaching criterion on learning trials, all groups performed at a similar level on subsequent way-finding.

3.3.4 Spontaneous strategy trials

3.3.4.1 Strategy types.

The spontaneous strategies used by participants on each of the four strategy trials during the test phase were grouped into four different categories. As in previous findings using VEs, (Bullens, Iglói, et al., 2010; Iglói et al., 2009), three of the strategies observed were (i) ‘Sequential Egocentric’ (3.2.2.1 Figure 9b), where participants repeated an identical sequence of body turns in both the normal and strategy tests; (ii)

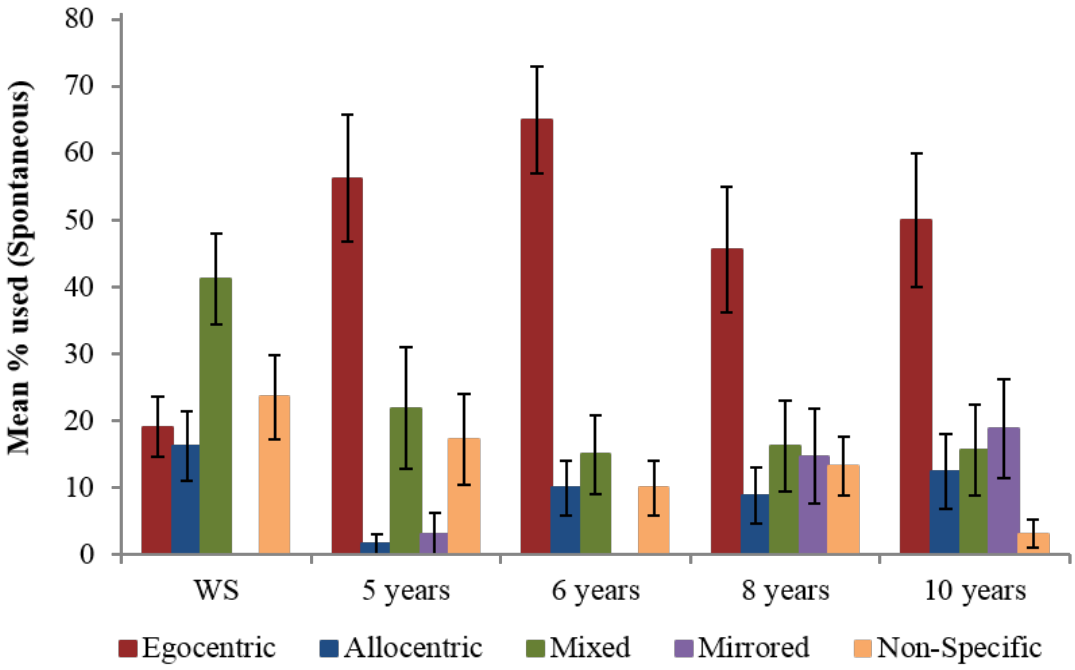
'Allocentric' (3.2.2.1 Figure 9c), where participants used environmental cues and an understanding of the environment layout to reach the correct hidden exit by the shortest route; and (iii) 'Mixed' (3.2.2.1 Figure 9d), where participants demonstrated a change from a sequential egocentric strategy at the start of the trial to the use of environmental cues within one trial. Some participants in the current study also demonstrated the use of a fourth strategy that has been labelled (iv) 'Mirrored Egocentric' (3.2.2.1 Figure 9e), where during the strategy tests participants traversed along a route towards the hidden target that was the mirror image of the 'sequential egocentric' route. This strategy potentially demonstrated an understanding of the symmetrical layout of the environment and thus an alternative route to the hidden exit, but without consideration of the positioning of landmarks. Participants who did not reach the hidden exit at the end of path D or G using any of these strategies, or who got lost during the spontaneous tests were allocated the category (v) 'non-specific' for those trials. Mean percentage of each type of strategy used across the four spontaneous strategy trials in each group, are displayed in 3.3.4.1.1 Figure 12.

Data were analysed to examine the differences between groups on the percentage of each strategy type used on spontaneous trials. As data did not meet normality assumptions (Kolmogorov-Smirnov, $p < .05$) for any groups, Kruskal- Wallis tests were conducted, with post-hoc Mann-Whitney tests. Results showed a significant difference across groups on percentage of egocentric strategy use, $\chi^2 (4) = 13.95$, $p = .007$, due to the WS group using an egocentric strategy significantly less often than all other groups (5 year-olds, $p = .006$; 6 year-olds, $p < .001$; 8 year-olds, $p = .048$; and 10 year-olds, $p = .026$). A significant difference across groups on percentage of mixed strategy use was also found, $\chi^2 (4) = 13.29$, $p = .010$, with individuals with WS using a mixed strategy significantly more often than all other groups (5 year-olds, $p = .025$; 6 year-olds, $p = .005$; 8 year-olds, $p = .006$ and 10 year-olds, $p = .004$). Results also showed a significant difference across groups on percentage of mirrored strategy use, $\chi^2 (4) = 14.63$, $p = .006$. Post-hoc tests showed that 10 year-olds used a mirrored strategy significantly more often than 5 year-olds ($p = .037$), 6 year-olds ($p = .010$), and WS ($p = .006$), and 8 year-olds used a mirrored strategy significantly more often than 6 year-

olds ($p = .048$) and WS ($p = .036$). No significant group differences were found on percentage of allocentric or non-specific strategies used ($p > .05$ for both).

Data were also analysed to examine whether one strategy was used significantly more often than any other within each group separately. Results of Friedman's ANOVAs, (5 levels; egocentric, allocentric, mixed, mirrored, and non-specific) showed a significant effect of strategy type used on spontaneous trials in all groups: 5 year-olds, $\chi^2(4) = 22.93$, $p < .001$; 6 year-olds, $\chi^2(4) = 29.43$, $p < .001$; 8 year-olds, $\chi^2(4) = 10.08$, $p = .039$; 10 year-olds, $\chi^2(4) = 15.30$, $p = .004$; and WS, $\chi^2(4) = 21.54$, $p < .001$. Post-hoc Wilcoxon Signed Ranks tests showed that this was due to a significantly greater percentage of egocentric compared to allocentric and non-specific strategies in all TD groups; 5 years ($p = .002$ and $p = .014$); 6 years ($p = .002$ and $p = .003$); 8 years ($p = .015$ and $p = .022$); and 10 years ($p = .023$ and $p = .003$). A significantly greater percentage of egocentric than mixed was found in 6 ($p = .007$) and 8 ($p = .043$) year-olds, and a significantly greater percentage of egocentric than mirrored for 5 and 6 year-olds ($p = .001$ for both). Only the 6 year-olds showed significantly less use of a mirrored strategy than allocentric ($p = .034$) or mixed ($p = .024$). In contrast, the WS group used a mixed strategy significantly more often than egocentric ($p = .030$), allocentric ($p = .041$) and mirrored ($p = .001$) strategies, and a mirrored strategy significantly less often than allocentric ($p = .015$) and non-specific ($p = .006$).

To examine the consistency of performance in each group across the four strategy trials, the percentage of participants who used the same strategy on at least three out of the four trials was calculated. The majority of participants in each of the TD groups were consistent in their use of strategy type (5 year-olds = 93.3%, 6 year-olds = 66.7%, 8 year-olds = 64.7%, and 10 year-olds = 75.0%). However, consistent strategy use across the four trials was not observed in participants with WS, with the majority of participants in this group (70.6%) using different strategies across trials.



3.3.4.1.1 Figure 12. Mean (SE) percentage of each strategy used across the four spontaneous strategy test trials in each group

3.3.4.2 'Allocentric score' on spontaneous trials.

To examine the extent to which participants in each group were navigating 'allocentrically' across the four spontaneous trials, an allocentric score was calculated for each participant. For each of the four spontaneous trials, zero points were awarded for the use of a sequential egocentric strategy, or non-specific strategy, and two points were given for each allocentric strategy used. Given that the use of a mixed strategy may have demonstrated a change from an egocentric to allocentric strategy within one trial, one point was awarded for each mixed strategy used. One point was also allocated for each mirrored egocentric trial as this may have resulted from an understanding of the shape of the environment, a component of allocentric knowledge. Participants could therefore receive a maximum score of eight allocentric points across the four spontaneous trials. Total allocentric score was then converted to a percentage for analysis, for comparison to the corresponding score for enforced-allocentric trials (see 3.3.5.2).

Data were normally distributed for 8 and 10 year-olds and WS groups only (Kolmogorov-Smirnov, p> .05). However, given that normality was present for more than half of the groups, and ANOVA can be robust to violations of normality assumptions, parametric tests are reported. Non-parametric equivalents of the following analyses were also conducted, with comparable results. The analysis showed a significant difference across groups on percentage allocentric score on spontaneous trials, due to a significantly higher allocentric score in the WS group than TD 5 (*p= .028*) and 6 year-olds (*p= .032*). Mean percentage allocentric score for each group and results of a one-way ANOVA are displayed in 3.3.4.2.1 Table 10.

3.3.4.2.1 Table 10. Mean (SD) percentage allocentric score on 'spontaneous' and 'enforced allocentric' trials across each group

	Group					One-way ANOVA		Post-hoc[a]
	WS (N=17)	5 years (N=16)	6 years (N=14)	8 years (N=17)	10 years (N=16)	F (df)	*p*	
[b]Spontan.	36.76 (18.47)	14.06 (20.35)	15.18 (18.46)	24.26 (20.48)	29.69 (28.46)	3.19 (4, 79)	*.018**	WS > 5 and 6
[c]Enforced	24.51 (11.96)	25.00 (32.06)	25.00 (19.06)	38.73 (22.81)	52.60 (31.58)	4.04 (4, 79)	*.005***	5 = 6 = WS < 10

[a] Tukey-corrected post-hoc tests, '=' refers to no significant difference at .05 level, and '<' denotes *p< .05*; [b] Spontaneous strategy trials; [c] Enforced allocentric trials. *significant at .05 level; **significant at .01 level.

3.3.5 Enforced allocentric trials

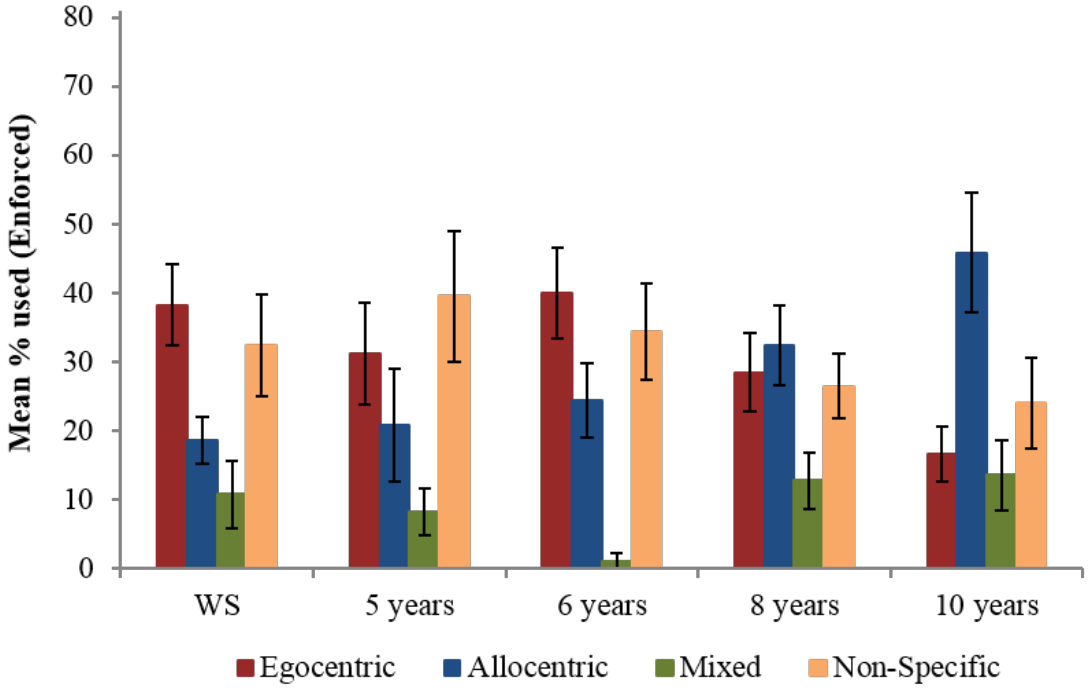
3.3.5.1 Strategy types.

The strategy used on each of the six enforced allocentric trials was identified for each participant. Strategies were identified in the same way as for the spontaneous

trials and consisted of sequential egocentric, allocentric, mixed, and non-specific strategies. For Mean percentage of each strategy-type used across the six enforced allocentric strategy trials see 3.3.5.1.1 Figure 13.

As for spontaneous trials, data were analysed to examine the differences between groups on the percentage of each strategy-type used during enforced trials. As data violated normality assumptions for all groups (Kolmogorov-Smirnov, $p < .05$), Kruskal- Wallis tests were conducted, with post-hoc Mann-Whitney tests. Results showed a significant difference across groups on percentage of egocentric strategies used, $\chi^2 (4) = 9.53$, $p = .049$, with 6 year-olds and WS groups using an egocentric strategy significantly more than 10 year-olds ($p = .006$ and $p = .009$, respectively). Results also showed a significant difference across groups on percentage allocentric strategy used, $\chi^2 (4) = 10.05$, $p = .040$, with 5 year-olds and WS groups using an allocentric strategy significantly less than 10 year-olds ($p = .013$ and $p = .014$, respectively).

To examine whether one strategy was used significantly more often than any other within each group separately, Friedman's ANOVAs (4 levels: egocentric, allocentric, mixed, or non-specific) were conducted. Results showed a significant difference between strategy type used during enforced trials in 6 year-olds, $\chi^2 (3) = 19.87$, $p < .001$, and WS, $\chi^2 (3) = 13.80$, $p = .003$ groups, and a trend in 5 year-olds, $\chi^2 (3) = 7.63$, $p = .054$. Post-hoc Wilcoxon Signed Ranks tests showed that for 6 year-olds, an egocentric strategy was used significantly more often than a mixed strategy ($p = .001$). Allocentric and non-specific strategies were also used more often than a mixed strategy in this group ($p = .007$ and $p = .003$, respectively). Similarly, 5 year-olds used an egocentric strategy significantly more often than a mixed strategy ($p = .016$). Individuals with WS however, demonstrated the use of an egocentric strategy significantly more often than mixed ($p = .006$) and allocentric ($p = .003$) strategies, both of which would have resulted in successful navigation to the hidden exit. The predominant use of egocentric searching during the enforced trials in WS was, therefore, indicative of an ineffective navigation strategy in this group.



3.3.5.1.1 Figure 13. Mean (SE) percentage of each strategy used across the six enforced allocentric test trials in each group

3.3.5.2 Allocentric score for enforced allocentric trials.

An allocentric score from the six enforced trials was calculated for each participant using the same criteria as for spontaneous trials. Participants could therefore receive a maximum score of 12 allocentric points across the six trials. As before, allocentric scores were then converted to percentages for analysis. Data were normally distributed for all groups, except TD 5 year-olds. However, given that normality was present for all but one of the groups in the sample, parametric tests are reported. Non-parametric equivalents of the following analyses were also conducted, with comparable results. Mean percentage allocentric score on enforced allocentric trials and results of a one-way ANOVA are displayed in 3.3.4.2.1 Table 10, showing a significant difference across groups, due to a significantly higher allocentric score in TD 10 year-olds than 5 year-olds ($p = .019$), 6 year-olds ($p = .012$) and WS group ($p = .014$).

Differences in allocentric score on spontaneous trials compared to enforced allocentric trials were examined. A two-way mixed ANOVA was performed on percentage allocentric score, with a between-participants factor of group (5 levels: 5, 6, 8, 10 and WS) and within-participants factor of trial type (2 levels: spontaneous or enforced). Results showed a significant main effect of group, $F(4, 75) = 3.94$, $p = .006$, partial $\eta^2 = .17$, and a significant main effect of trial type, $F(1, 75) = 7.72$, $p = .007$, partial $\eta^2 = .09$. A significant interaction was also identified, $F(4, 75) = 3.27$, $p = .016$, partial $\eta^2 = .15$. Results of post-hoc paired-samples t-tests for each group showed a significant increase in allocentric score from spontaneous to enforced trials for TD 8 year-olds, $t(16) = -2.39$, $p = .029$ and TD 10 year-olds, $t(15) = -2.40$, $p = .030$. In contrast, a significant decrease in allocentric score was demonstrated in participants with WS, $t(16) = 2.24$, $p = .040$. No significant difference was found for 5 or 6 year-olds.

To determine whether there were any effects of gender, spontaneous and enforced allocentric scores for males and females were also compared. Results found no significant differences between males and females on spontaneous or enforced allocentric scores in any group ($p > .05$ for all).

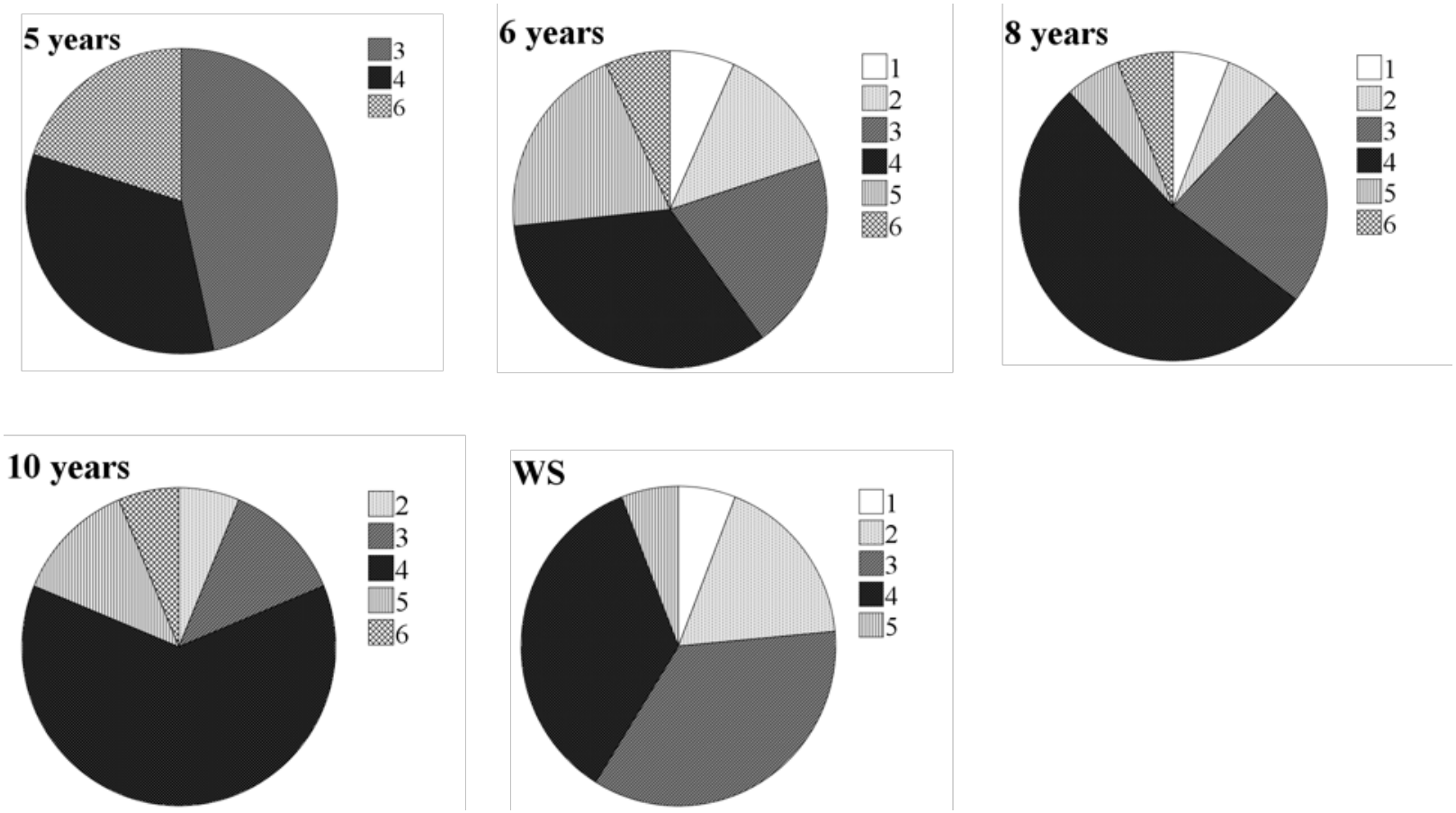
3.3.6 Layout knowledge test

The correct layout from a choice of six was chosen by 31.3% of participants in the 5 year-old group, 33.3% of 6 year-olds, 52.9% of 8 year-olds, 62.5% of 10 year-olds, and 35.3% of participants with WS. Even the oldest TD children did not, therefore, perform at an exceptionally high level on this task. However, this is in line with what could be expected based on the percentage of older TD participants who were able to successfully employ either an allocentric or mixed navigation strategy on enforced trials (8 year-olds = 45.1%, and 10 year-olds = 59.4%).

Performance in each group was compared to the level that would be expected due to chance (16.67%). Results of chi-squared tests showed no significant difference from chance among 5 year-olds, 6 year-olds, or participants with WS, ($p > .05$ for all).

In contrast, the correct layout was chosen significantly more often than chance in 8 year-olds χ^2 (1) = 5.11, *p*= *.024*, and 10 year-olds, χ^2 (1) = 7.54, *p*= *.006*. For proportion of each maze layout option, including the correct choice (layout 4) chosen by participants in each group, see 3.3.6.1 Figure 14.

Independent samples t-tests were used to examine whether children in the oldest two TD groups who chose the correct layout had higher allocentric scores than those who chose the incorrect layout. The results found that TD 10 year-olds who chose the correct layout had significantly higher percentage 'enforced allocentric' scores (correct: Mean = 66.67, SD= 30.17; incorrect: Mean = 29.17, SD= 17.28), than those who were incorrect, t(13.99) = 3.16, *p*= *.007*. No significant differences were found for spontaneous allocentric scores, or for either allocentric scores in TD 8 year-olds (p > *.05* for all).



3.3.6.1 Figure 14. Proportions of each maze layout option chosen by participants in each group

3.3.7 Relationships between allocentric score, age and cognitive abilities

Given the wide age-range in the WS group, it may have been that older participants with WS were more likely to use an allocentric strategy than younger participants with WS, due to greater life-experience in navigating, and thus increased opportunities to develop a more efficient navigation strategy. Furthermore, chronological age in WS was positively related to object-based mental rotation ability in study 1 (see 2.3.7), suggesting that some spatial abilities may develop with age in individuals with WS. Therefore, the relationships between age and allocentric scores were calculated for each group. Given the small sample sizes in relation to results of power analyses discussed in Chapter 2 (suggested N = 21), data were collapsed across TD age groups. Data were normally distributed for TD and WS groups (Kolmogorov-Smirnov, $p > .05$), and so Pearsons correlations were used.

Results showed that, although age was significantly correlated with both spontaneous and enforced allocentric score in the TD group when collapsed across age groups (spontaneous, $r(63) = .28$, $p = .024$; enforced, $r(63) = .39$, $p = .002$), no significant relationships were found for any TD group separately ($p > .05$ for all), nor between age and allocentric scores in the WS group ($p > .05$ for both).

As allocentric ability was not correlated with chronological age in any group, the relationship between performance on verbal and non-verbal cognitive measures and ability to employ an allocentric strategy during navigation was also examined. Correlations were calculated for each group separately between BPVS-III and RCPM raw scores and both spontaneous- and enforced-allocentric scores. Results showed that for 6 year-olds, percentage enforced allocentric score was significantly positively related to BPVS-III raw score, $r(15) = .67$, $p = .010$. Conversely, for 10 year-olds, the percentage enforced allocentric score was significantly positively related to RCPM raw score, $r(16) = .65$, $p = .007$. No other significant correlations were found in 5 year-olds, 8 year-olds and WS groups ($p > .05$ for all).

3.4 Discussion

The aim of this study was to examine navigation strategies employed in a large-scale virtual environment, by typically-developing children aged 5–10 years and individuals with Williams syndrome. The study examined the strategies that were employed spontaneously during navigation and also the ability to use an allocentric strategy on trials that required an understanding of interrelationships between features within the environment and a representation of the environmental layout.

The types of strategies used to navigate through the cross-maze were in line with those identified in previous studies of similar design (Bullens, Iglói, et al., 2010; Iglói et al., 2009). In particular, TD children between 5 and 10 years predominantly relied on the use of a sequential egocentric strategy –retracing the same sequence of body turns – to navigate through a route. The results also identified some spontaneous use of allocentric strategies, particularly in the older TD children, and an increase with age in the spontaneous use of a mirrored strategy, indicative of an increasing sophistication in the use of different spatial frames of reference with development. This, in turn, suggests that the use of a mirrored strategy was a reflection of partial allocentric knowledge, rather than a backwards re-tracing of the route from the end to the start. Backwards retracing would have reflected a misunderstanding of the task instructions and thus would be more likely seen in the youngest TD group.

These findings also reflect performance seen in typical adults (Iglói et al., 2009), suggesting that from at least 5 years of age, a predominant reliance on the use of an egocentric strategy during basic way-finding in a familiar environment does not go through a significant developmental change. The results did, however, highlight a developmental increase in the ability to employ an allocentric spatial strategy when navigation required an understanding of the spatial relationships between environmental locations. This is indicative of an age-related increase in the ability to encode more complex spatial information for successful and efficient navigation. During enforced allocentric trials where participants were required to encode the spatial relationships within the environment, independent of previously experienced viewpoints, only 8 and

10 year-old TD children showed a reliable use of this spatial ability. In contrast to this, Bullens, Iglói, et al. (2010) showed above chance performance on allocentric spatial tasks in TD children as young as 5 and 6 years. Although the current cross-maze was designed as a less complex environment than that used in previous studies, including fewer decision points, our results may be a reflection of more stringent scoring criteria, with trials counted as incorrect when a participant made incorrect initial turns or returning later to a correct path following indirect exploration. This is reflected in the high number of incorrect ('non-specific') trials performed across groups. However, the more stringent scoring criteria used in the current study is likely to more accurately bring to light the ability of each participant to use an allocentric strategy from the starting point of a trial, without error; thus, producing a clearer summary of performance.

The findings from the layout choice test also show that only the oldest TD participants were able to accurately select the correct layout more often than chance, indicative of having developed an allocentric spatial representation of the environment. Indeed, this was reflected in significantly higher enforced-allocentric scores in TD 10 year-olds who correctly chose the layout compared to those who made an incorrect selection. The second highest choice across all groups was the alternative square layout with four paths, suggesting that participants in each group had developed some understanding of the basic shape of the environment. However, given that this was the most commonly selected layout by individuals in the youngest TD and WS groups, the conceptualisation of traversing and making turns around a square-shaped route may have been the most prominent and important feature for these participants, rather than the correct global spatial representation that would have taken into account all aspects of the environmental layout.

In addition to replicating previous findings in TD children, these results provide insight into the nature of large-scale spatial navigation in WS. Individuals with WS were able to successfully learn a route through the environment after a similar number of trials as TD children between 5 and 8 years of age. This is in line with previous

route-learning studies, in which individuals with WS were able to learn a route sequence and recall this successfully after a few attempts, albeit at a slower rate than TD children (e.g., Farran et al., 2010; Farran, Courbois, Van Herwegen, & Blades, 2012). Therefore, although route-learning may be impaired relative to chronological age in WS, the performance of individuals with this disorder is in line with TD children of similar non-verbal ability.

In contrast to route-learning ability in WS, trials examining the type of spontaneous strategies used during wayfinding highlighted an atypical pattern of performance in this group. Unlike TD children, for whom a sequential egocentric strategy was predominantly employed, individuals with WS primarily demonstrated the use of a mixed strategy. On such trials, it could be surmised that participants began by using a body-based sequential egocentric strategy to navigate, but then switched to using environmental landmarks as a guide to the correct path. Use of this strategy could therefore be a reflection of a change from an egocentric to allocentric strategy within one trial, following the late realisation of a change in starting position. As a consequence, in the calculation of an 'allocentric score', participants were rewarded for partial use of an allocentric strategy when this occurred. This therefore elucidates the high allocentric score on spontaneous trials in the WS group relative to TD groups. Two possible explanations could be put forward for this finding in WS. Firstly, it may have been that participants with WS were more able than TD children to spontaneously switch to using an allocentric strategy to find the correct path. Secondly, an alternative explanation is that individuals with WS would start by relying on the use of a sequential egocentric strategy, but then following a difficulty in determining subsequent turns, would switch to using a view-matching strategy, relying on perceptual matching of visual scenes of distant landmarks to guide navigation. If the first turn made by participants in the WS group was due to random choice, there would likely be an equal number of 'mixed' and 'allocentric' strategies reported during spontaneous strategy trials. However, the higher proportion of 'mixed' strategies in this group is indicative of the ability to remember only the initial egocentric turn. It should be noted however, that a 'mixed' strategy was not used consistently across the four strategy trials in this

group. Therefore, although this may have been the predominant strategy used in the WS group, inconsistency by participants with WS on this task suggests a more unsystematic and extemporary approach to navigation.

Poor performance in WS on 'enforced allocentric' trials that required the use of an allocentric navigation strategy for success, also suggest that the use of a mixed strategy on spontaneous trials was unlikely to be a reflection of allocentric spatial knowledge in this group. Indeed, participants with WS presented with a significantly lower allocentric score on enforced trials compared to spontaneous trials. This indicates that although landmarks are significantly utilised in guiding the retracing of a route in WS (conceivably through the use of a view-matching strategy), developing a representation of the interrelationships between landmarks and the location of the exit following movement of the self, may be particularly problematic.

This use of a mixed strategy and possible switch to a reliance on view-matching was less evident, however, on enforced trials. This may have been due to difficulties in switching from an egocentric to view-matching strategy when beginning from multiple starting places on these trials. Alternatively, the second route may not have been consolidated as well as the first, and therefore been under competition from the previously learnt route. However, this is unlikely as participants in all groups successfully learnt the second route before continuing onto the enforced allocentric trials. These findings raise a question as to whether individuals with WS would perform successfully during an enforced egocentric task, or have difficulties in the use of a sequential egocentric strategy; a concept that will be examined further in study 4.

Allocentric coding difficulties in WS are in line with previous results from both small (e.g., Bernardino et al., 2013; Nardini et al., 2008) and large-scale (Farran et al., 2010) tasks, and findings of atypical search strategies and difficulties developing a cognitive spatial map in real-world tasks (Foti et al., 2011). Even adults with WS have difficulties in understanding the intrinsic spatial relationships between landmarks within an array (Nardini et al., 2008), despite it being seen to develop in TD children as young as 5 years of age. Similarly, impairments in the use of both egocentric and allocentric

frames of reference in WS were identified using 3D spatial judgment tasks (Bernardino et al., 2013).

Given the multiple opportunities to navigate the VE in this study, allocentric spatial coding difficulties in WS are unlikely to be due to reduced navigation experience, as seen in typical development (e.g. Anooshian & Young, 1981; Lehnung et al., 2003; Siegel & White, 1975). As such, it is unlikely that poor performance on large-scale tasks requiring relational knowledge in previous studies (Farran et al., 2010) would have been alleviated with continued environmental experience. Indeed, even potential navigation experience gained throughout development in individuals with WS was not conducive to superior allocentric coding abilities, as seen in the lack of reliable association between chronological age and allocentric scores in this group.

Findings from spontaneous trials in particular suggest a greater unprompted reliance on landmarks in WS than in TD children, who showed a predominant use of a strategy that did not take into account the presence of landmarks. This reliance on such a rudimentary view-matching approach to wayfinding in WS may be related to underlying difficulties in spatial working memory, previously noted in WS (Mandolesi et al., 2009; Vicari, Bellucci, & Carlesimo, 2003; Vicari et al., 2006). The use of a sequential egocentric strategy relies on the ability to continuously update the location of the self in reference to the starting position both temporally and spatially, and is hence supported by spatial working memory. Research examining the use of landmarks during navigation in WS, alongside performance on perceptual view-matching tasks would, therefore, further explicate the spontaneous strategies relied on in WS. Poor performance on perceptual-matching tasks would demonstrate difficulties in recalling and visually matching patterns, and would thus rule out view-matching as a possible way-finding strategy; however, findings suggest that perceptual matching may be relatively unimpaired in WS (Hoffman et al., 2003). Indeed, Vicari et al. (2006) found that performance in WS was in-line with mental-age matched controls on a perceptual object matching task, but not on a perceptual spatial orientation task, suggesting that

different perceptual abilities may be differentially affected in WS, particularly when a spatial element is included in a task.

Results from spontaneous and enforced trials in this study imply that processing of both allocentric *and* egocentric spatial codes may be atypical in WS. Even though route-learning ability was in line with TD children of similar non-verbal ability, the differential use of strategies during navigation compared to the same group of TD children suggests that this is not simply a reflection of developmental delay in WS, but of a differential developmental trajectory. It is likely, therefore, that individuals with WS use alternative compensatory strategies to navigate, often resulting in inefficient search techniques.

Difficulties in the use of egocentric spatial coding are in line with a particular vulnerability of the parietal portion of the dorsal stream known to be associated with WS (e.g. J. Atkinson & Braddick, 2011; J. Atkinson et al., 1997; Meyer-Lindenberg et al., 2004). In typical development, the dorsal visual stream is specialised for the guidance of action (Milner & Goodale, 1995), and the atypical development of the dorsal stream in WS is thought to be an enduring feature across development, persisting into adulthood (J. Atkinson et al., 2006). Activation of the left hippocampus also plays a role in the use of a sequential egocentric representation during navigation (Iglói et al., 2010). Vulnerability of the hippocampus in WS (Meyer-Lindenberg et al., 2005) is therefore likely to contribute to impairments in episodic memory, namely, difficulties in retracing the complete sequence of turns through an environment identified in this group.

One study examining large-scale spatial search in two individuals with WS and two patients with a partial genetic deletion on the WS critical region of chromosome 7q11.23, also alludes to difficulties in the coding of egocentric spatial information in WS (Smith, Gilchrist, Hood, Tassabehji, & Karmiloff-Smith, 2009). The authors found that, in comparison to the inefficient search strategies seen in WS, the partial deletion patients did not demonstrate such difficulties, despite the deletion of the LIM domain kinase 1 (*LIMK1*) gene, which has been previously implicated in spatial deficits in WS

(e.g. Frangiskakis et al., 1996). As such, difficulties observed with egocentric spatial coding in WS may arise from a combination of deleted genes within the WS critical region, which in-turn impinges upon the development of brain regions that typically subserve such cognitive functions. This will be explored further in study 5, through the presentation of two individuals with contrasting partial deletions on 7q11.23.

Turning to allocentric coding and the associated role of the hippocampus (e.g. Iaria et al., 2007; Iglói et al., 2010; King et al., 2002), impairments in global spatial representations are also in line with known atypical function and metabolism of this region in WS (Meyer-Lindenberg et al., 2005). This said, the ability to update the location of the self following movement within an allocentric frame of reference is thought to rely on successful translation between egocentric and allocentric spatial codes supported by the parietal and retrosplenial regions (including the hippocampus), respectively (Burgess, 2008; Lambrey et al., 2012; Vann et al., 2009). Therefore, attributing the difficulties in egocentric and allocentric spatial coding in WS to deficits in individual brain regions may be somewhat simplistic, and a more detailed understanding of the relationships between behaviour and atypical functioning in these brain areas in WS is required. Further studies involving functional brain imaging during large-scale navigation tasks in WS may help to elucidate the specific cortical mechanisms associated with the performance and types of navigation strategies employed in this group.

Impairments in the ability to encode large-scale space in relation to both egocentric and allocentric spatial reference frames indicate that it may not only be the more complex spatial tasks that pose a challenge for individuals with WS. It is unclear, however, whether the use of view-matching and reliance on landmarks during navigation in WS is the result of an atypical spontaneous strategy, or whether this has been taught as a compensatory strategy to some individuals. Further examination of this and the development of navigation abilities with age and experience in WS may provide insight into possible interventions to enhance the use of more efficient navigation strategies. This said, no relationship was found between age, or cognitive

ability, and allocentric score in WS in this study, and so it may be unlikely that experience and age are influencing factors in increased navigational ability in this group. However, an examination of the reliance on landmarks in WS compared to TD children during route learning may provide insight into whether this is an important strategy for individuals with this disorder.

3.5 Conclusions

In summary, the results of this study indicate that during spontaneous navigation through a familiar environment, TD children between 5 and 10 years of age predominantly rely on the use of a sequential egocentric strategy. Individuals with WS, however, primarily employ an atypical navigation strategy, which likely involves an early switch from the use of an egocentric strategy to a reliance on the perceptual properties of visual landmark scenes in an environment as indicators to the correct pathway. On trials that required an understanding of the spatial relationships between landmarks in the environment, however, only TD children aged 8-10 years demonstrated the ability to use an allocentric strategy and develop a global mental representation of the environmental layout. These results are indicative of deficits both in allocentric *and* sequential egocentric spatial coding in WS, even following extensive experience in an environment, resulting in the use of more time-consuming and less efficient strategies for way-finding in large-scale environments. Specific inferences that can be made from the findings of this study bring into question whether individuals with WS are able to develop a sequential egocentric representation of a route. Indeed, if not, do individuals with WS rely heavily on the presence of landmarks and visual cues to orientate and locate their goal; and to a greater extent even than TD children? A further investigation of this in study 4 may provide important insight not only into the specific impairments that individuals with WS have when navigating through large-scale environments, but also the strategies and methods that are preferably relied upon in this group.

Chapter 4

Study 3: The relationship between small and large-scale spatial abilities in typical development and Williams syndrome

4.1 Introduction

For the most part, research into spatial cognition, and particularly the field of Williams syndrome research, has examined small-scale visuospatial abilities separately from performance on large-scale tasks. Despite spatial cognition at different scales being considered somewhat dissociable, performance on small-scale spatial tasks is often used to make inferences about cognition and processing in large-scale space (D.R. Montello, 1993). However, the relationships between these aspects of spatial cognition, and thus the underlying determinants of large-scale spatial knowledge, are not clearly understood. Different reports have been offered regarding the extent to which performance on tests in small-scale space account for the variance in spatial ability on large-scale environmental tasks. Predominantly, these studies have correlated small-scale, table-top measures of spatial cognition with large-scale measures such as route-knowledge or way-finding ability (e.g., Pearson & Ialongo, 1986; Thorndyke & Goldin, 1983). Some authors have noted substantial correlations, as high as r =.57 (Walsh, Krauss, & Regnier, 1981) and even .88 (Vandenberg & Kuse, 1978). However, in a review of the literature examining the link between table-top psychometric test performance and large-scale spatial abilities, Hegarty and Waller (2005) found predominantly very weak correlations (around r = .2) reported by the majority of authors.

Support for a robust relationship between spatial abilities at different scales therefore is ambiguous. However, differences in study outcomes and generally poor levels of predictability may be due to the use of different spatial measures at both scales, and with disparate cognitive factors likely to underlie different large-scale spatial abilities (Allen et al., 1996; Hegarty et al., 2006). For example, navigational abilities

may be differentially related to aspects of visuospatial cognition, depending on the type of spatial information and mental imagery required for each task.

As discussed in study 1, a distinction can be made between cognitive processes required for the mental manipulation of objects and those for imagined self-rotations (see also, Huttenlocher & Presson, 1979). Research has therefore sought to examine the relationships between these different mental imagery skills and different aspects of environmental spatial cognition. As discussed more thoroughly in 1.3, in typical adults, the ability to mentally rotate a geometric shape and imagine the self moving through an environment are related to an ability to form a mental representation of the spatial relationships between landmarks and update the location of the self within this cognitive map (Palermo et al., 2008). Similarly, visual perspective-taking ability in adults reliably predicts navigational abilities, particularly on tasks that required the individual to keep track of their changing position in relation to environmental objects (Kozhevnikov et al., 2006). Conversely, the authors of this study did not find a reliable relationship between mental rotation and navigational performance.

Other research has also identified relationships between different cognitive processing strategies on small-scale tasks and the ability to successfully develop route (also called way-finding) knowledge compared to allocentric (also called survey/cognitive-map/global) knowledge (e.g., Thorndyke & Hayes-Roth, 1982). For instance, individuals who are able to successfully develop survey representations of large-scale space outperform 'landmark-centred' navigators on tests of mental rotation (Pazzaglia & De Beni, 2001), with others showing that route and survey encoding are preferentially related to perspective-taking and object-based rotations, respectively (Fields & Shelton, 2006). Brain imaging studies provide further insight into the possible relationships between cognitive processes involved in tasks at different spatial scales, although these are scarce (however see, Shelton and Gabrieli (2004).

In developmental research, although some studies have failed to identify significant correlations between small and large-scale spatial tasks (Quaiser-Pohl et al., 2004), a link between performance on tests of visuospatial ability (including mental

rotation, Corsi block and mental paper folding tests) and way-finding in a real-world environment was found in children aged 5-6 years, but not for older children aged 7-9 years of age (Fenner et al., 2000). Fenner et al. found that young children with a low score on tests of visuospatial ability made significantly more errors than those of higher visuospatial ability, a pattern not shown in the older children. This suggests that younger children rely on different cognitive strategies to support navigation, which are more related to the small-scale visuospatial abilities examined in that study. Fenner and colleagues concluded that older children may have developed more efficient cognitive strategies for way-finding that do not rely on visuospatial cognition, as measured on these small-scale tasks. On examining this further, Purser et al. (2012) found that although a significant association was found between standardised measures of visuospatial working memory and large-scale route-learning ability in children aged 5-11 years, these relationships were largely moderated by executive control, suggesting that caution should be taken when interpreting correlations between tasks when they may both be mediated by other cognitive demands.

Despite these few developmental studies, the extent to which object-based (OB) mental rotation and visual perspective-taking (VPT) are differentially related to large-scale navigation abilities across development, as seen in typical adults (e.g., Kozhevnikov et al., 2006), remains unclear. Developmental changes in the way in which OB rotation and VPT tasks are performed (e.g., Huttenlocher & Presson, 1973; Newcombe & Huttenlocher, 1992), and also the maturation of the ability to integrate different spatial frames of reference to support navigation (Bullens, Iglói, et al., 2010; Nardini et al., 2006), suggests that there may be different underlying mechanisms involved in spatial cognition across development. In typical adults, a linear increase in reaction time is observed with increased angular disparity on object-based mental rotation tasks, but not on visual perspective-taking tasks (e.g., Zacks et al., 2000). In typically developing (TD) children however, this angular disparity effect *is* observed during perspective-taking tasks (Roberts & Aman, 1993), demonstrating that children use a different technique to perform self-rotations compared to adults, who are able to employ a more 'automatic' transformation to complete these tasks (Wraga et al., 2000;

Zacks & Michelon, 2005). Indeed, in typical adults an advantage for spatial memory in terms of performance and reaction time is found following imagined rotation of the self compared to equivalent array-rotations (Lambrey et al., 2012). As such, developmental changes in the cognitive processes involved in these small-scale tasks may result in the emergence of different techniques to mentally update the position of the self in large-scale space during navigation with age.

With regards to individuals with WS, little can be concluded thus far as to the possible relationships between spatial abilities at different scales. In one study, Farran et al. (2010) examined the relationships between route-learning performance in individuals with WS compared to TD controls, and performance on small-scale tasks that included visuospatial working memory, VPT, and map use. Results showed that performance on small-scale tasks was not related to real-world navigation abilities in TD children. In the WS group and a group of individuals with moderate learning difficulty, a measure of visuospatial working memory where participants were asked to draw a route through a maze previously seen on an image in front of them, correlated with large-scale route knowledge (number of correct turns made retracing a route) and relational knowledge (pointing to imperceptible landmarks). However, associations between other small and large-scale spatial abilities were not seen, and as a group, poor performance on the maze task contrasted with relatively good route-learning, suggesting that impairments on tasks at different spatial scales are not necessarily indicative of a single deficit in WS.

In the present chapter, the relationships between performance on a more comprehensive set of measures of small-scale mental rotation and visual perspective-taking (study 1) and large-scale route-learning and ability to use an allocentric strategy for navigation (study 2) were examined. The present analyses were conducted to further identify the extent to which similar cognitive mechanisms may support the capacity to perform imagined mental rotations of objects and the self on small-scale tasks and different aspects of large-scale navigation in TD children aged 5-10 years and individuals with WS. As discussed above, in typical adults, some inferences can be

made as to large-scale spatial abilities or individual preferences for specific navigational strategies from performance on different small-scale measures of mental imagery (Fields & Shelton, 2006; Kozhevnikov & Hegarty, 2001; Pazzaglia & De Beni, 2001). Therefore, an investigation into the relationships between such tasks in WS and across typical development may provide important insight into whether impairments across different spatial scales should be considered independent, or are likely supported by common underlying mechanisms, such as the ability to employ different spatial frames of reference, in these groups. This would have important implications, particularly for research in WS, regarding the extent to which findings of impairments on table-top visuospatial tasks could be used to make inferences about deficits in large-scale space.

The development of an ability to successfully employ the use of an allocentric spatial frame of reference between 8 and 10 years of age in a large-scale virtual environment (study 2), alongside near-ceiling performance on measures of object-based mental rotation and visual perspective-taking (study 1), suggest that older children perform more in line with typical adults on these different measures of spatial cognition than younger children. That said, caution should be taken in interpreting the ceiling performance on measures of OB mental rotation and VPT, reported in study 1, as having reached adult level, given the lack of an adult control group and possible lack of sensitivity of the tasks to measure a full range of ability. However, the navigation strategies employed in the oldest TD group in study 2 are similar to those seen in typical adults on comparable tasks (Iglói et al., 2009), and suggest a developmental change in the ability to apply an appropriate spatial frame of reference between 5 and 10 years of age. Given that positive correlations are identified between performance on different measures of mental transformation (imagined rotation of objects or the self) with route-learning and ability to use an allocentric strategy in adults (e.g., Kozhevnikov & Hegarty, 2001), it can be inferred that performance on these types of small- and large-scale spatial measures will similarly correlate in older children between 8 and 10 years of age. However, the pattern of performance on tasks at different spatial scales in younger TD children and individuals with WS and whether similar cognitive mechanisms are involved across tasks remains unclear.

4.2 Methods

4.2.1. Participants

For the present analysis, only participants who completed all four mental transformation tasks from study 1 (visual perspective-taking (VPT) path, object-based (OB) monkey task, VPT circle, and OB circle) and navigation strategies tasks from study 2 were included. Sixty-one TD children were therefore included and separated into the same four age-groups as noted in studies 1 and 2: 5 year-olds (N=15, 9 males, Mean age (years; months) = 5;06 years, SD = 0;03, CA range = 5;01 – 6;01); 6 year-olds (N=14, 10 males, M_{age} = 6;08 years, SD = 0;03, CA range = 6;04 – 7;05); 8 year-olds (N= 16, 9 males, M_{age} = 8;03 years, SD = 0;04, CA range = 7;07 – 8;08); and 10 year-olds (N=16, 9 males, M_{age} = 10;01 years, SD = 0;03, CA range = 9;06 – 10;07). Participants with WS who completed all tasks in study 1 and 2 (N=16, 8 males, M_{age} = 22;05 years, SD = 8;04, CA range = 13;01 – 43;03) were also included.

4.2.2. Design and procedure

All participants completed the four mental rotation tasks in the order stipulated in study 1 (see 2.2.6) before completing the spatial navigation tasks. All participants with WS who were included in the present analysis completed testing in one day, with breaks given when necessary. Given that the majority of testing in the TD groups was conducted during school time and at the participant's school, tasks were separated into two shorter sessions to be completed within one month (mean = 19.02 days (16.83)).

For full task designs for the four mental rotation measures and spatial navigation tasks, see corresponding Method 2.2 and 3.2. In brief, participants were asked to complete two visual perspective-taking (VPT) tasks to examine the ability to imagine the rotation of the self on a single axis (VPT path task) and the rotation of the self to various displacements around an array (VPT circle task), and two object-based (OB) mental rotation tasks to examine ability to imagine the rotation of a single object on one axis (OB monkey task) and the rotation of objects in an array (OB circle task). This

allowed for a full range of OB mental rotation and VPT abilities to be examined. On the spatial navigation task, participants were asked to learn a route in a VE cross-maze. They were then tested on their spontaneous navigation strategy and their ability to use an allocentric strategy when required to take the shortest route from new starting places in the environment.

4.2.3. Variables

Comparisons were conducted between variables in each main group (TD and WS) and each TD age group separately (TD 5, 6, 8 and 10 year-olds). For the four small-scale measures, percentage rotation trials correct on VPT path and OB monkey tasks and percentage left-right trials correct on VPT circle and OB circle tasks were used. From the large-scale VE navigation paradigm, variables included 'route-learning' (the cumulative number of errors across learning trials) and 'way-finding' (after having reached learning criterion, the number of correct trials from the test phase, excluding the 4 'spontaneous test trials'). 'Enforced allocentric score' was used as a measure of large-scale relational knowledge. Given the small group sizes and non-normally distributed data (kolmogorov-smirnov, $p < .05$), non-parametric Spearman's correlations were conducted.

4.3 Results

4.3.1. Small-scale spatial abilities and large-scale route-learning and way-finding

To determine the relationship between small-scale visuospatial ability and large-scale route-learning and way-finding, comparisons were carried out for each group between performance on the four mental rotation trials and number of errors across learning trials (route-learning), and number of correct test trials following learning (way-finding).

As mentioned in Chapter 2 and 3, given the small sample sizes in relation to results of power analyses (suggested N = 21), data were first collapsed across TD age groups. When collapsing across TD groups and controlling for age, significant correlations were only found between performance on the VPT path and 'wayfinding' (r (57)= .28, *p= .035*), and between OB circle performance and route-learning (r (57)= .32, *p = .013*).

On examination of relationships between tasks across each group separately, a significant relationship was found between large-scale route-learning and performance on the OB circle task in TD 6 year-olds, r_s (14)= -.66, *p*= .010, and TD 10 year-olds, r_s (16)= -.54, *p= .033*, and between route-learning and VPT path task in TD 8 year-olds, r_s (14) = -.52, *p= .041,* and TD 10 year-olds, r_s (16) = -.54, *p= .032*. No other comparisons between performance on small-scale tasks and route-learning were significant in any other group (*p > .05* for all).

Comparisons between large-scale way-finding performance and small-scale tasks yielded significant relationships only in TD 10 year-olds between number of correct test trials and OB circle, r_s (16) = .54, *p= .031*. No other comparisons were significant in any other group *(p > .05* for all). For full results of correlational analyses, see **4.3.2.1 Table *11***.

4.3.2. Small-scale spatial abilities and large-scale allocentric knowledge

To examine whether performance on small-scale tasks were related to large-scale spatial relational knowledge, comparisons were carried out between the four small-scale mental rotation measures and percentage enforced allocentric score. This variable was used as this provided the most accurate indicator of participants' ability to use an allocentric strategy to navigate in a large-scale environment when required. Non-parametric comparisons yielded a significant relationship between performance on the two VPT tasks and allocentric score in the TD 10 year-olds, in the predicted direction; VPT path: r_s (16) = .72, *p= .002* and VPT circle: r_s (16) = .63, *p= .009*.

4.3.2.1 Table 11. Non-parametric correlations between small and large-scale spatial abilities for each group

Group			VPT path[a]	OB monkey[b]	VPT circle[c]	OB circle[d]
5 yrs	Route learning[e]	r_s	.23	-.09	-.18	-.11
		p	*.41*	*.75*	*.53*	*.71*
	Wayfinding correct[f]	r_s	.47	-.04	.16	-.22
		p	*.08*	*.89*	*.58*	*.43*
	Allo score[g]	r_s	-.15	-.12	.04	-.25
		p	*.59*	*.70*	*.88*	*.36*
6 yrs	Route learning	r_s	-.04	-.35	-.41	**-.66**
		p	*.89*	*.22*	*.15*	***.01***
	Wayfinding correct	r_s	.17	.16	-.21	.12
		p	*.56*	*.59*	*.46*	*.69*
	Allo score	r_s	-.06	.29	.24	.10
		p	*.83*	*.32*	*.42*	*.73*
8 yrs	Route learning	r_s	**-.52**	.06	.43	-.28
		p	***.04****	*.84*	*.10*	*.30*
	Wayfinding correct	r_s	-.08	.19	.16	.05
		p	*.78*	*.49*	*.55*	*.86*
	Allo score	r_s	-.38	.02	.09	-.09
		p	*.14*	*.93*	*.75*	*.74*
10 yrs	Route learning	r_s	**-.54**	-.29	-.17	**-.54**
		p	***.03****	*.27*	*.52*	***.03****
	Wayfinding correct	r_s	.45	.26	.38	**.54**
		p	*.08*	*.33*	*.15*	***.03****
	Allo score	r_s	**.72**	.18	**.63**	.37
		p	***<.01****	*.49*	***.01****	*.15*
WS	Route learning	r_s	.04	.44	-.23	.05
		p	*.88*	*.09*	*.39*	*.86*
	Wayfinding correct	r_s	.07	.06	-.25	.32
		p	*.79*	*.82*	*.35*	*.25*
	Allo score	r_s	-.21	-.15	-.09	.25
		p	*.43*	*.59*	*.75*	*.37*

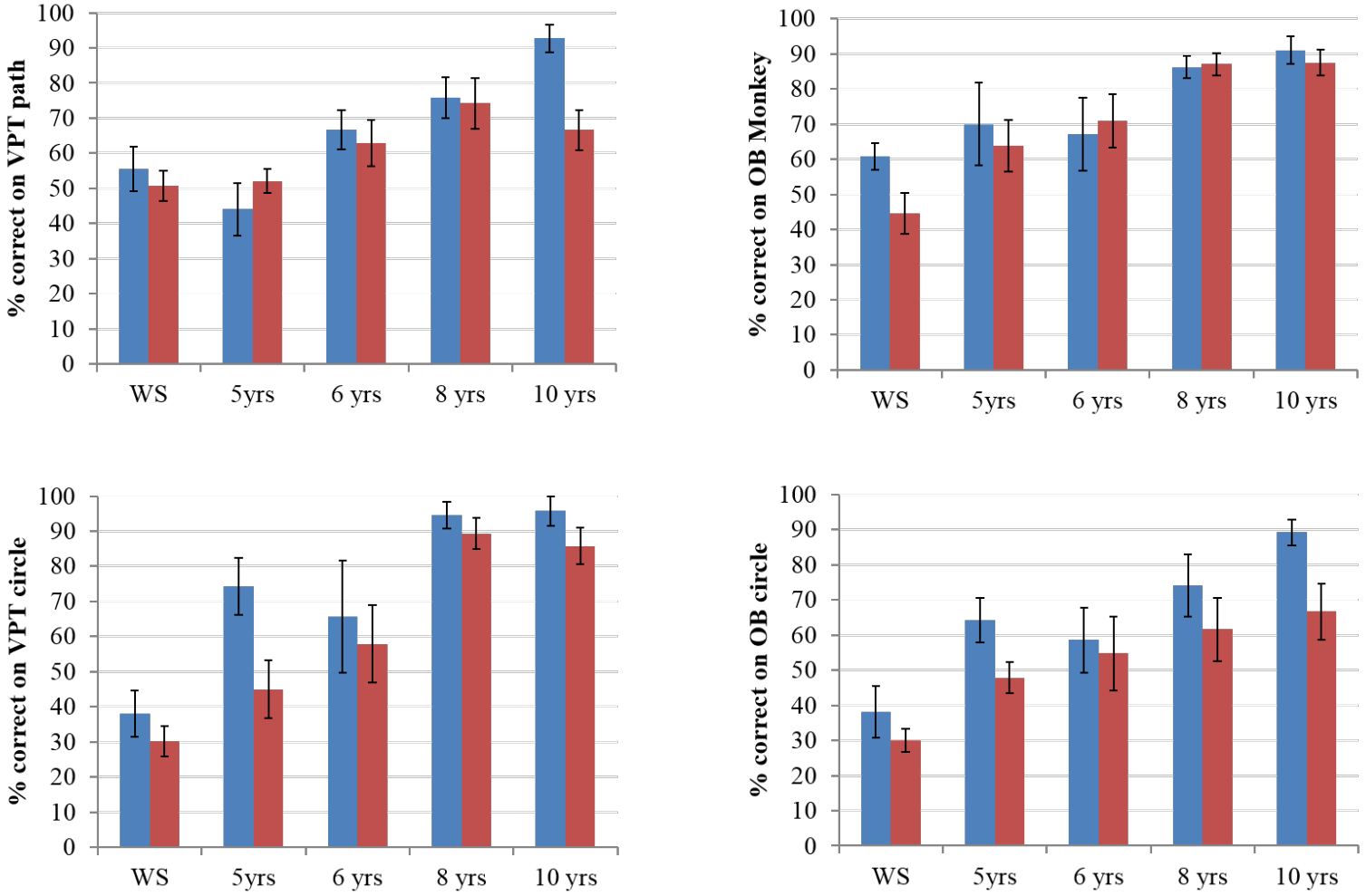
* = significant at .05 level, ** = significant at .01 level. [a]Percentage correct on VPT path, [b]percentage correct rotation trials on PB monkey task, [c]percentage correct left-right trials on VPT circle task, [d]percentage correct left-right trials on PB circle task, [e]cumulative number of errors on route-learning trials, [f]total correct wayfinding trials, [g]percentage enforced allocentric score.

4.3.3. Small-scale spatial abilities and layout knowledge test

To further examine associations between small-scale spatial abilities and large-scale spatial relational knowledge, performance on small-scale tasks by participants

who correctly identified the spatial layout and those who did not, were compared in each group. Participants in each group were separated into subgroups of those who selected the correct layout option on the 'layout knowledge test' and those who chose an incorrect option. Given the small and unequal subgroup sizes, non-parametric Mann-Whitney tests were conducted to compare mean scores on each mental transformation test between correct and incorrect subgroup participants in each group separately. Descriptive statistics are displayed in 4.3.3.1 Figure 15.

Significant differences in mean scores were found between 'correct' and 'incorrect' subgroups on the VPT maze, VPT circle and OB circle, in TD 10 year-olds only (VPT maze: U= 5.50, $p= .005$; VPT circle: U= 15.00, $p= .048$; and OB circle: U= 9.50, $p= .024$). No significant difference between subgroups in TD 10 year-olds was found on the OB monkey task ($p> .05$). No significant differences between subgroups on mental transformation scores were found for any other group ($p> .05$ for all).



4.3.3.1 Figure 15. Mean (SE) percentage score on the four mental transformation tasks for layout test subgroups (correct [blue]/ incorrect [red]) in each group

4.4 Discussion

The extent to which object-based mental rotation and visual perspective-taking are differentially related to large-scale navigation abilities in TD children and individuals with WS was examined in this chapter. The results revealed significant correlations between route-learning performance in a large-scale environment and the ability to mentally rotate objects around a small-scale array (OB circle task) in TD 6 and 10 year-olds, and the ability to imagine the self rotating on a single axis (VPT path) in TD 10 year-olds. Way-finding ability on a previously-learnt route was associated with performance on the OB circle task only in the TD 10 year-old group. Comparatively, large-scale allocentric knowledge positively correlated with both small-scale measures of VPT in the oldest TD group, indicative of a large amount of shared variance between imagining the self moving on a single axis and around an array, and the ability to develop a mental representation of the spatial relationships in a large-scale environment at 10 years of age. This was further supported as TD 10 year-olds who chose the correct environmental layout (a test of large-scale allocentric spatial knowledge) performed at a significantly higher level on the two VPT tasks than those who chose an incorrect layout. No reliable associations between performances on tasks at different spatial scales were found in the WS group, a discussion of which will follow an examination of the findings across typical development.

Previous developmental studies regarding the extent to which small-scale spatial abilities are related to performance on spatial tasks at an environmental scale have shown mixed results. In one study, a significantly greater number of environmental route-learning errors were made by TD 5-6 year olds with low compared to high visuospatial ability, a finding not seen in older TD children aged 7-9 years (Fenner et al., 2000). However, although the study by Fenner and colleagues included visuospatial measures such as mental rotation, spatial short-term memory span, and a mental paper-folding task, an aggregate visuospatial score was calculated from these sub-tests and individual spatial skills were not examined separately. A more multifaceted view of visuospatial cognition was taken in the current analyses, and the findings suggest that

different large-scale spatial abilities in children are associated with disparate aspects of small-scale spatial cognition, not just with visuospatial cognition *per se*. In particular, the ability to mentally rotate the position of shapes around an array was reliably associated both with learning a new route in an environment in 6 and 10 year-olds, and re-tracing a familiar route having previously reached learning criterion in 10 year-olds. Of note however is the lack of reliable correlations in TD 5 and 8 year-olds on these tasks alongside significant findings in the TD 6 and 10 year-olds. In typical adults, mental rotation abilities have been found to be associated with a preference for survey-based (allocentric) encoding, but not with better route learning performance, as seen in TD 6 and 10 year-olds in this chapter (Fields & Shelton, 2006; Pazzaglia & De Beni, 2001; Shelton & Gabrieli, 2004). The contrasting findings presented here may reflect a difference in strategy use for learning a route in children compared to adults that suggests similar cognitive demands are involved in imagined array-rotation and route-learning during development, but not by adulthood. However, little is known about the neural correlates of spatial encoding at small and large scales across development, and so our understanding of the possible shared mechanisms underlying mental rotation abilities and different aspects of navigational performance in typical children compared to adults remains limited. If mental rotation is indeed a robust predictor of route-learning performance in TD children, the small group sizes in this study may be a contributing factor to the lack of reliable findings across all TD groups (as indicated by the *a priori* power analyses). Further research with larger sample sizes across groups should therefore be conducted before robust conclusions can be met regarding the extent to which OB mental rotation is associated with environmental route-learning across this period of development.

Other developmental studies have been unsuccessful in finding a relationship between small-scale spatial abilities and environmental knowledge in children (Quaiser-Pohl et al., 2004). Here, the authors reported no correlations between measures of small-scale spatial cognition (spatial object-perception and mental rotation) and configurational (allocentric) knowledge as measured by neighbourhood sketch-maps

drawn by children aged 9-12 years. This finding was, in part, reflected in the current analysis, with no significant associations found between measures of OB mental rotation and allocentric knowledge in any group. However, in the oldest TD group, individuals who selected the correct environmental layout were significantly better at mentally rotating objects around an array. On one hand, this may indicate that (in older TD children) this small-scale ability shares more similar underlying mechanisms with large-scale allocentric knowledge than classic mental rotation of a single object as measured by the OB monkey task in the current analysis and those used by Quaiser-Pohl and colleagues. However, a lack of relationship with the OB monkey task in this chapter is more likely a reflection of near-ceiling performance on this task by 8 and 10 year-olds. Alternatively therefore, the current findings can be considered as reflecting the relationship between OB rotation abilities and 'map-like' or survey encoding of an environment seen in typical adults (Fields & Shelton, 2006; Pazzaglia & De Beni, 2001; Shelton & Gabrieli, 2004), by 10 years of age.

Until now, studies examining associations between cognitive abilities at different spatial scales in TD children have not included measures of VPT (although see Farran et al., 2010). Strong positive correlations between performance on both VPT tasks and allocentric score in TD 10 year-olds in the current analyses suggest that small-scale VPT may be a more reliable predictor of individual and developmental differences in large-scale spatial abilities, and particularly allocentric knowledge, than OB mental rotation. This pattern of performance in TD 10 year-olds is in line with adult data, which indicates that VPT ability is positively related to performance on navigational tasks that require updating self-to-object representations, more than the variance predicted by mental rotation measures (Kozhevnikov et al., 2006). Indeed, Palermo and colleagues (2008) similarly found that the ability to develop a cognitive map was related to the ability to imagine the self moving through an environment, as measured in a task similar to the VPT path task used here.

It is logical to surmise that similar cognitive mechanisms are employed during the use of an allocentric navigation strategy, which allows for the recognition of

environmental landmarks and their relative location given a change in viewer perspective, and imagining what an array of objects would look like following a change in position, as measured in small-scale VPT tasks. Neuroimaging studies support the finding of an association between these two cognitive abilities. For instance, preferential activation of the parieto-occipital sulcus (including retrosplenial cortex) and left anterior hippocampus are seen in tasks requiring imagined self-rotation compared to object/array-based mental rotation (Lambrey et al., 2012); a finding consistent with cortical activation that is often associated with spatial navigation (e.g., Maguire, 2001) and the 'spatial updating' of egocentric locations (supported by the posterior parietal lobe) within an allocentric environmental frame of reference (supported by hippocampal and medial temporal lobe structures) (Vann et al., 2009). In essence, comparable brain regions are seen to subserve imagined self-rotations and the ability to update the location of the self following movement in small and large-scale space, respectively.

Why then is the association between VPT and allocentric ability not also observed in TD children younger than 10 years of age? The ability to infer spatial relationships between elements in an environment that are independent of the viewer's initial perspective develops between 6 and 8 years (Nardini et al., 2009), suggesting that children of this age possess the mental operations by which they are able to imagine themselves at a different viewpoint. However, no relationship between imagined self-rotations (on the VPT tasks) and allocentric knowledge was found in the current chapter in these age groups. As such, the representation of spatial relationships between objects in an array may not be akin to developing a representation of a whole space allocentrically. Development of the ability to switch successfully between egocentric and allocentric navigation strategies is protracted, with adult-like performance not occurring until 10 years (Bullens, Iglói, et al., 2010; see also study 2). This, alongside a similar developmental course for performing imagined transformations of the self (see study 2) more feasibly underlies the lack of association between VPT and navigation abilities in TD children before this age. As such, the use of a successful strategy on the

allocentric navigation tasks in children below 10 years may be accounted for by different processing to that used by older children and adults.

Immature executive functioning, particularly inhibition, may also contribute to difficulties in strategy-switching during navigation in younger children, as seen in other spatial cognitive tasks (Davidson, Amso, Anderson, & Diamond, 2006), and in inhibiting an egocentric response in VPT tasks. Proficiency on tasks of inhibition is dependent on the frontal lobes, which are considered to have an extended developmental course (Diamond, 1990). Purser et al. (2012) found that correlations between performance on measures of visuospatial short-term memory and route-learning in school-age children were mediated by aspects of executive function indexed by a 'Go/No-Go' task , even when controlling for chronological age. This may therefore support the findings of shared variance between small and large-scale measures in older TD children, but not in younger children who have poorer inhibitory control.

In the analyses conducted in this chapter, no significant correlations were found between performance on any spatial tasks at different scales in the WS group. Given that differences in performance across VPT and OB tasks are reported between TD and WS groups (see section 2.3), and that some reliable associations between small and large-scale measures (particularly in TD 10 year-olds) were found, the tasks used in this study can be considered valid and reliable measures of different components of visuospatial cognition. As such, the lack of significant relationships between task performances in the WS group across any measures warrants an alternative explanation. Performance at the level of chance on imagined rotations of objects and the self at rotations greater than 45º from vantage point in WS may partly elucidate the lack of associations in this group. However, despite poor group performances on the majority of imagined rotations on VPT and OB tasks in the WS group, all WS participants were able to learn a route, and to a similar extent to TD children of comparable non-verbal ability. Furthermore, performance on the OB monkey task in WS was found to correlate significantly with chronological age, even when controlling for verbal and

non-verbal ability (see 2.3.7) indicative of variability in spatial ability in WS. On measures of large-scale spatial cognition however, variation in performances within the WS group reflected a more inconsistent and unsystematic approach to navigation rather than strategic behaviour seen in (particularly older) TD children.

These findings suggest that, although no reliable correlations are seen between performance on small and large-scale spatial tasks, not all spatial skills are compromised to the same extent in WS; particularly in regards to large-scale spatial cognition, where route-learning abilities may not be as compromised as spatial relational coding. Furthermore, just because impairments in WS are seen on small-scale spatial tasks, it is not parsimonious to assume that these difficulties will translate to large-scale space. This was echoed by Farran and colleagues (2010), who found minimal correlations between small and large-scale abilities in individuals with WS, concluding that impairments in WS on small and large-scale tasks are indicative of independent deficits at each level.

4.5 Conclusions

The findings presented in this chapter, alongside those from previous research, have important implications for understanding spatial cognition both in typical development and WS. In TD children, aspects of large-scale spatial cognition that consist of route-learning and way-finding abilities are reliably associated with the ability to imagine the rotation of an array of objects. However, this was not a finding that was consistently found across each age group, and is in contrast with results from typical adults. More reliable relationships however were found between performance on small-scale VPT tasks and allocentric ability at a large scale in TD 10 year-olds, a finding that is in line with performance and shared variance between such tasks in adults. In the WS group, no significant relationships were found between abilities at different spatial scales, indicative of high levels of inconsistency in performance on spatial tasks in this group. Therefore, although there may be common mechanisms underlying some small- and large-scale abilities in TD children by 10 years of age

(particularly when both tasks require the ability to update the location of the self following imagined or actual movement and thus translating between egocentric and allocentric reference frames), this is not the case for younger TD children or individuals with WS. As such, in the same way that aspects of small-scale spatial cognition such as OB mental rotation and VPT should be considered as distinct abilities, supported by independent mechanisms, so too should aspects of spatial cognition measured at different scales. To some extent there are likely to be commonalities in the underlying mechanisms and indeed overlapping neural correlates of small and large-scale visuospatial cognition; however, it is not true to say that performance at one spatial scale would reliably predict performance at another.

Chapter 5

Study 4: Sequential egocentric navigation and reliance on landmarks in typical development and Williams syndrome

5.1. Introduction

The findings reported in study 2 of this thesis suggest that the development of global representations of space, and the use of allocentric spatial strategies to guide navigation are particularly problematic for individuals with WS. This extends previous findings of impairments in the use of an allocentric spatial frame of reference in WS both on small-scale (Bernardino et al., 2013; Nardini et al., 2008) and large-scale tasks (Farran et al., 2010). Similar difficulties in developing an understanding of the global layout of an environment -for use in devising short-cuts- have also been found in some individuals with intellectual difficulties (Mengue-Topio et al., 2010) and Down syndrome (Courbois et al., 2013), and suggests that atypical brain development can often result in a reliance on more simple spatial learning strategies such as associating landmark cues with a specific egocentric response.

Atypical navigational performance during spontaneous way-finding tasks in individuals with WS also indicates that the use of more simple sequential egocentric strategies (as predominately used in TD children and adults) may be problematic for this group (see study 2). These findings suggest instead that individuals with WS may rely on less efficient navigation strategies. One possibility, explored in this chapter, is that this group use a strategy that involves searching for familiar visual scenes in order to find a target location.

In previous studies, including the findings from study 2, individuals with WS have been found to successfully learn a route both in virtual and real environments, albeit often at a slower rate than TD children of comparable non-verbal ability (Farran et al., 2010; Farran, Courbois, Van Herwegen, & Blades, 2012; Farran, Courbois, Van Herwegen, Cruickshank, & Blades, 2012). However, to date, this has only been

examined in environments in which landmarks have been present. As such, research into the extent to which individuals with WS rely upon the presence of landmarks to guide learning and the retracing of a route would provide further insight into the specific navigation strategies that are commonly employed in this group. More specifically, an examination into the ability to use a sequential egocentric strategy when explicitly required to do so (for example, when landmarks are removed and an individual must rely on their memory of the sequence of left-right body turns) would be a useful tool to further identify specific deficits in large-scale spatial cognition in WS.

In the real world, navigation usually requires the ability to retrace a route from one location to another, along familiar or previously learnt paths, only occasionally necessitating knowledge of short-cuts or an understanding of the spatial relationships between locations in a given environment. Indeed, some research has argued that even when taking novel short-cuts, a more simple landmark navigation strategy is predominantly employed, rather than complex allocentric spatial referencing (Foo, Duchon, Warren, & Tarr, 2007; Foo et al., 2005). Given the importance of egocentric spatial coding and the use of landmarks as navigational guides, therefore, it is essential to address the way in which individuals with WS are able to navigate from one location to another along familiar routes, and which aspects of the environment are the most useful in aiding successful way-finding.

5.1.1. The role of landmarks in navigation

Landmarks are typically defined as features that serve as spatial 'points-of-reference' (Lynch, 1960), with others purporting that these points of reference must be easily recognisable and memorable in order to serve a useful function with regards to spatial cognition (Presson & Montello, 1988). However, the *extent* to which landmarks are used to facilitate route-learning and the specific function that they serve, has been a matter of some debate. Research in typical adults regarding the specific role of landmarks has found contrasting results. Some authors have reported the importance of environmental landmarks as navigational aids (e.g., Jansen-Osmann, 2002), while

others have found little benefit of the presence of landmarks, particularly when other strategies, such as recalling a sequence of left-right turns, are readily available to the navigator (e.g., Tlauka & Wilson, 1994).

Through a series of experiments, Waller and Lippa (2007) found that the impact of landmarks on way-finding abilities depends largely on the purpose that landmarks serve during learning, with landmarks that are used as 'beacons' (e.g., when a landmark is located near to a particular goal, prompting the individual to simply navigate towards it) resulting in more accurate learning and subsequent way-finding than those functioning as 'associative cues' (when a landmark is paired with a particular directional action such as 'turn left at the tree'). The authors relate this distinction between the use of 'beacons' and 'associative cues' to that made between recognition memory and cued-recall memory tasks, respectively; with recognition tasks being less complex and cognitively demanding than cued-recall. Others have also found that the nature of landmark knowledge depends on the type of navigational experience. For instance, L. Wang, Mou, and Sun (2013) found that after only one trial to learn a route, participants could develop landmark knowledge for guidance (akin to Waller and Lippa's (2007) 'landmarks as beacons'), but that the use of landmarks for place recognition (likened to 'landmarks as associative-cues') or knowledge of landmark sequence developed after retracing the route five times. As such, these findings imply that the visual cues that are utilised from a given environment for navigation, and indeed the function that they serve, is likely to be context-specific and dependent on the demands of the task.

Another distinction in the type of environmental landmark that could be utilised to support navigation lies in whether it is a global (distal) landmark, which can be seen from multiple locations around and within the environment, or a local (proximal) landmark, which can only be seen from one locality. In typical adults, slight detriments to the accuracy of way-finding can be seen when either of these types of landmarks are removed (Steck & Mallot, 2000) (although see, Purser et al., in press). However, compared to a no-landmark condition, errors in way-finding were only reduced

following the inclusion of local, but not global landmarks (Ruddle, Volkova, Mohler, & Bülthoff, 2011), indicating that there was no additive effect of having both forms of landmark available, and that the orientation information that global landmarks provided did not have a beneficial effect.

Given that the use of proximal landmarks in way-finding studies may only support the use of paired-associative learning (Waller & Lippa, 2007; L. Wang et al., 2013), the use of distal landmarks instead could encourage the development of more complex spatial knowledge for navigation. In study 2, distal landmarks were used to encourage the development of allocentric mental representations of space, but also allowed for the use of a sequential egocentric representation as a spontaneous navigation strategy in TD children. For consistency, distal landmarks were also used in the present study, to encourage the use of similar cognitive mechanisms and spontaneous navigation strategies. Indeed, the presence of distal landmarks as presented here would allow for the use of paired-associative learning, but not limit way-finding to this strategy. The additive benefits to way-finding of including both proximal and distal landmarks is unclear. Some research has reported no additional benefit for including proximal alongside distal landmarks (Ruddle et al., 2011), whilst others find improved performance with the inclusion of both (Purser et al., in press). In light of this, and for consistency with study 2, proximal landmarks were not included in this study.

5.1.2. The use of landmarks across development

The ability to use landmarks to guide performance on spatial tasks develops throughout early childhood (e.g., Newcombe & Huttenlocher, 2000; Sutton, 2006), although a range of ages have been suggested as to when the ability to use different landmarks emerges, which is likely reflected in the variability of task demands and size of environmental space. In relation to the development of spatial knowledge for navigating in large-scale environments, spatial representations become progressively more complex throughout childhood, with landmark knowledge conjectured to precede sequential route knowledge and global or configurational mental representations,

respectively (Cousins et al., 1983; Siegel & White, 1975). This developmental acquisition of spatial knowledge is considered to be mediated by the emergence of low-level cognitive abilities, with landmark knowledge associated with the development of recognition-in-context memory, and route knowledge with the emergence of paired-associative learning (Allen & Ondracek, 1995). Others have concluded that these age-related changes are associated with a development of spatial coding, rather than a qualitative shift from one stage to the next (e.g., Newcombe & Huttenlocher, 2000). This is also in line with different developmental trajectories for egocentric and allocentric spatial frames of reference as seen in both small- (Nardini et al., 2006) and large-scale tasks (Bullens, Iglói, et al., 2010), with older children and adults more able to successfully switch to using an allocentric frame of reference when the task requires a more global mental representation of space.

It can be inferred, therefore, that younger children will rely on more basic landmark-based spatial strategies by which to navigate, that do not comprise of allocentric (spatial-relational) information. Indeed, Cohen and Schuepfer (1980) showed children aged 7 and 11 years and adults a series of slides along a route that contained landmarks. Although all groups required the same amount of time to learn the route, when shown the slides of the maze without landmarks, 7 year-olds made more incorrect turn choices than 11 year-olds, who in turn made more errors than adults. The youngest children also recalled fewer landmarks that were integral to route orientation (i.e. positioned at a correct or incorrect turn), suggesting that younger children are more influenced by the place-connectivity induced by the presence of landmarks. These findings were replicated in the same age groups using continuous navigation through virtual environments (Jansen-Osmann & Wiedenbauer, 2004). Specifically, Jansen-Osmann and Fuchs found that although 11 year-olds and adults were able to learn a route in fewer trials than 7 year-old children (both with and without landmarks), route-finding performance in all groups benefited equally from the presence of landmarks. This suggests that young children did not rely more heavily on the existence of landmarks for way-finding. However, Jansen-Osmann and Fuchs (2006) argued that the

findings of the two aforementioned studies actually indicate that children and adults use landmark information in a qualitatively similar way to enhance way-finding, and that developmental differences in the use of landmarks are only seen in relation to other aspects of spatial cognition. For instance, when landmarks were part of a single semantic category, children aged 7-8 years were better able to *recall* landmarks that were adjoining correct turns than older children aged 11, and adults. However, the younger children were poorer at *locating* categorically similar landmarks. Thus, despite the importance of landmarks being shared by children and adults, younger children may be less able to integrate landmark location information into the development of a spatial representation of the environment.

The type of landmarks used may also vary across development. In line with this, when asked to retrace a route, children aged 6 and 12 years of age were found to benefit equally from being advised to take notice of landmarks near the route; although only the older children were able to benefit from being told to pay attention to distant landmarks (Cornell et al., 1989). As such, children and adults are seen to use the information provided by (proximal) landmarks to a similar extent to adults for way-finding behaviour, but that a developmental difference is seen in the way in which landmarks are used for other aspects of large-scale spatial cognition, with age-related differences in the use of landmarks dependent on the task demands and type of landmark available.

5.1.3. The role of landmarks in WS

To date, there has been a paucity of research examining the role of landmarks in navigation in WS. As mentioned previously, even adults with WS show deficits in understanding the intrinsic relationships between landmarks within a small-scale array (Nardini et al., 2008), a finding consistent with difficulties coding interrelationships between environmental features in large-scale space (as seen in study 2). However, on way-finding tasks in a 6-turn virtual environment, individuals with WS were able to successfully learn a route, using landmarks as cues to aid way-finding, in line with TD children aged 6-8 years (Farran, Courbois, Van Herwegen, & Blades, 2012). In

addition, Farran and colleagues found that individuals with WS with higher non-verbal ability were able to differentiate between junction and path landmarks, shown by superior memory for junction over path landmarks; indicative of an ability to understand the usefulness of landmarks at junctions. As a result, the authors concluded that although individuals with WS are able to form cognitive representations of landmarks, important landmark knowledge that can be used to enhance way-finding may only occur with increased maturity of non-verbal ability.

These findings suggest that environmental landmarks may play an important role in the development of spatial knowledge in WS, as seen in typical development. Furthermore, the findings reported from study 2 in this thesis indicate that individuals with WS may well use visual scenes within an environment to navigate, including in situations where TD children are able to apply alternative spatial coding strategies. The extent to which individuals with WS would rely on the presence of landmarks both for learning and retracing a route compared to TD children, however, remains equivocal.

One explanation for the findings in study 2 regarding the atypical strategies in WS on spontaneous navigation trials is that of a difficulty in using a sequential egocentric strategy to reiterate the same temporal sequence of body turns to retrace a route. Difficulties in recalling the specific sequence of turns in an environment may be in line with findings of a specific deficit in procedural learning in WS (Vicari, Bellucci, & Carlesimo, 2001). Vicari and colleagues identified procedural memory difficulties in WS shown by poor implicit learning of the temporal sequence of events on a serial reaction time block task. This deficit was not found in individuals with Down syndrome in a previous study (Vicari, Bellucci, & Carlesimo, 2000), suggesting that the procedural difficulties in WS are unlikely due to global cognitive delay, but are specific to the nature of brain and cognitive development in this disorder. This is in line with findings by Mandolesi et al (2009) using a radial arm maze, that demonstrated specific deficits both in procedural competencies and spatial memory in WS. Procedural memory will be assessed in the current study by examining the pattern of performance across junctions (1-6) in a 6-turn maze.

5.1.4. Neural basis of sequential egocentric navigation

The use of functional neuroimaging studies in typical adults has provided considerable insight into the neural correlates of different cognitive processes involved in the use of spatial navigation strategies, such as the encoding of interrelationships between environmental features, or the representation of body-based spatial coding. A greater understanding of the neural underpinnings of different navigation strategies has further identified not only the dissociation between body-based and environment-based representations of space, but also the way in which these systems overlap, and their association with different neural mechanisms for memory processes and motion-based mental representations. An overview of studies examining the neural basis of 'egocentric' and 'allocentric' processing can be found in chapter 3.

In brief, studies regarding 'allocentric' processing often highlight the role of the right hippocampal region (e.g., Burgess et al., 2002; Hartley et al., 2003), with 'egocentric' processing associated with activation in the fronto-parietal networks along the dorsal stream (e.g., Seubert, Humphreys, Muller, & Gramann, 2008; Weniger et al., 2009) and striatum (e.g., Packard and McGaugh, 1996). However, memory for the sequence of body turns associated with specific choice points through a route (a sequential egocentric strategy) may involve other neural networks than those associated with independent egocentric responses. Indeed, processing involved in the use of a sequential egocentric strategy may be akin to episodic memory processes (Iglói et al., 2009), with similar activation observed in the left hippocampus during such tasks (Iglói et al., 2010). Similarly, mentally navigating between landmarks on a previously learnt route is associated with activation in the insula and medial part of the hippocampal region (Ghaem et al., 1997), and sequential memory is associated with activation in the hippocampus, particularly during the acquisition of spatial sequences (Rolls & Kesner, 2006). These findings are in line with cortical activation during sequential route-based navigation in mice (Rondi-Reig et al., 2006). Furthermore, continued rehearsal of the same sequence of bodily turns during route-learning leads to the formation of a predominantly action-based mental representation that is associated with activation in

parietal/somatosensory, premotor cortex, and supplementary motor areas (Hartley et al., 2003).

In light of the findings regarding the neural basis of the use of different spatial frames of reference and navigational strategies, alongside findings of atypical brain development in WS, particularly in the hippocampus (Meyer-Lindenberg et al., 2005), it stands to reason that individuals with WS would exhibit specific difficulties on tasks requiring accurate processing of both allocentric and sequential egocentric spatial information. However, it remains unclear as to the strategies that individuals with WS typically use to complete way-finding tasks, and indeed, the underlying neural mechanisms and cortical structures that are involved.

5.1.5 Aims and hypotheses

The aim of this study was to examine the extent to which individuals with WS rely on the presence of landmarks both when learning a route, and when retracing a route once landmarks are removed following learning, compared to typically developing children of comparable verbal and non-verbal ability. In essence, are individuals with WS able to apply the use of a sequential egocentric strategy (recalling the sequence of left-right body turns), which is independent of the use of landmarks, to retrace a route when visual properties of the environment (i.e. landmarks) are no longer, or have never been, available?

Given the use of atypical strategies during spontaneous navigation tasks in WS (study 2), and the points discussed above, it can be inferred that individuals with WS will have difficulties in developing a sequential egocentric representation of a route, that could be used when landmarks are removed. Typically-developing children and adults are able to reiterate the sequence of body turns through a route to reach a target location (Bullens, Iglói, et al., 2010; Iglói et al., 2009). However, deficits in procedural memory and atypical brain development in cortical regions that subserve spatial coding strategies such as allocentric and sequential egocentric representations in WS imply that

individuals with this disorder will rely on landmarks, and to a greater extent even than TD children when learning a route. Impairments in the use of a sequential egocentric strategy would also be reflected in a difficulty learning a route that does not contain any visual landmark cues, and would therefore be indicative of a complete reliance on landmarks to guide way-finding.

With regards to the nature of difficulties in the use of a sequential egocentric strategy in WS, a further aim of this study was to examine the pattern and type of errors made by individuals with WS compared to TD children when learning routes in environments with and without landmarks, as a measure of procedural memory. That is, do individuals with WS present with a similar pattern of errors across junctions throughout environments with and without landmarks as seen in TD children?

5.2 Methods

5.2.1. Participants

Fifty-three typically developing (TD) children were recruited from two London, UK primary schools, and separated into three age groups; 5, 7, and 9 year-olds. Twenty-one individuals with WS were recruited from the records of the Williams Syndrome Foundation, UK. All participants with WS had received a positive diagnosis of WS, based on a "fluorescence *in-situ* hybridisation" (FISH) test for deleted Elastin gene on the long arm of chromosome 7, as well as phenotypic diagnosis from a clinician.

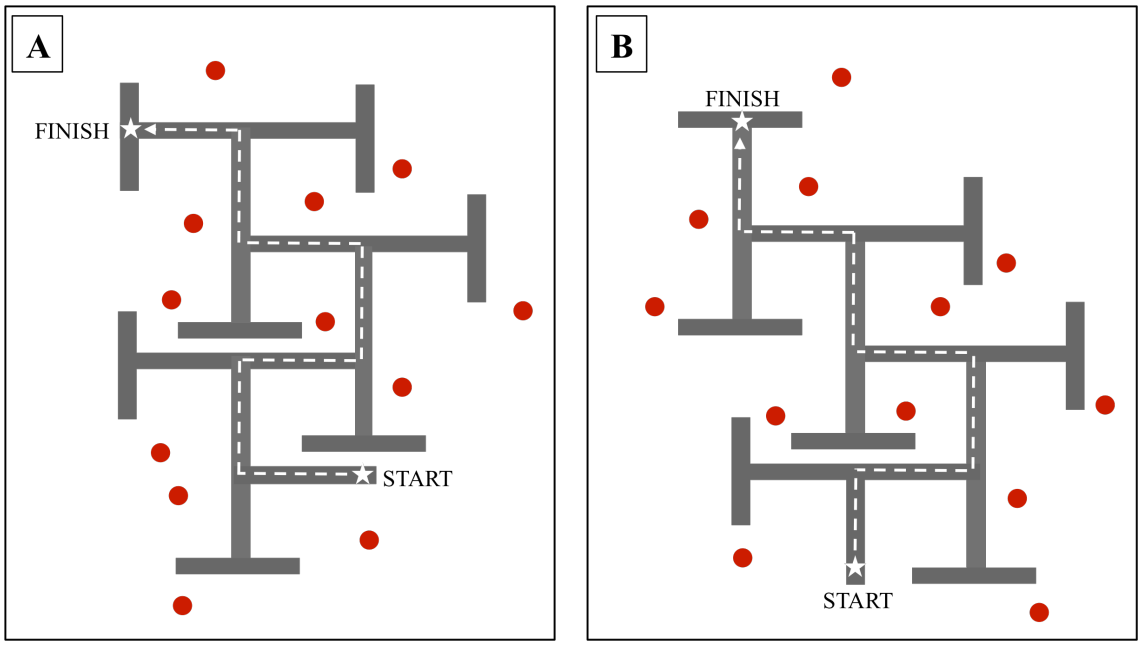
All TD participants were tested in a quiet room within their schools, whilst WS participants were tested either at their home or in a testing room at the Institute of Education, London. Seven participants from the TD groups; 5 years (N=5), 7 years (N=1), and 9 years (N=1), and three participants from the WS group had difficulties with the tasks or did not complete all measures. Data for these participants were subsequently excluded from the analyses. Therefore, data were analysed from 48 TD children; 5 years (N=16, 8 males, Mean age (years; months) = 5;09, SD= 0;02, CA range = 5;03–6;01); 7 years (N=16, 6 males, M_{age} = 7;08, SD= 0;02, CA range = 7;05–

8;00); 9 years (N=16, 8 males, M_{age} = 9;07, SD= 0;03, CA range = 9;03–10;00); and 18 participants with WS (9 males, M_{age} = 21;09, SD = 4;07; CA range = 16;01–32;01). Verbal and Non-verbal abilities were assessed using the British Picture Vocabulary Scale-III (BPVS-III; Dunn et al., 2009) and the Ravens Coloured Progressive Matrices (RCPM; Raven et al., 2003), respectively.

5.2.2. Virtual environment (VE)

The interactive virtual environment (VE) was developed using The Vizard Development Edition (version 3.0) software programme, and presented on a 17" laptop screen. The VE task presented participants with a 6-turn maze layout within which individuals were able to navigate using the arrow keys on the keyboard. Each path was of equal length, and each decision point consisted of a single left-right T-junction. Incorrect turns were also concealed by using T-junctions at the end of each dead-end path, so that they did not appear visually different from correct turns when viewed from the decision point. Each participant completed a 'landmark (LM)' and 'no-landmarks (NLM)' condition, the order of which was counterbalanced across participants in all groups. Two maze designs (layouts A and B) were employed; these contained identical path lengths, structure, and wall height, but with different sequences of left-right turns (see 5.2.2.1 Figure 16). To control for any differences across maze designs, half of the participants in each group received layout A as the LM condition and layout B as the NLM condition, whilst the other half received layout B as the LM condition and layout A as the NLM condition. For consistency, the same set of landmarks was used for each LM condition, regardless of maze design (A or B), with comparable configurations.

To distinguish between conditions and encourage participants to learn a different route, the LM condition always consisted of red-brick walls, whereas the NLM condition maze always contained grey-brick walls, regardless of whether layout A or B was used. This was kept consistent for all participants so that LM scenes presented in a 'visual matching' task (detailed in section 5.2.3.4.), that was presented following the LM trials, all contained red brick walls.



5.2.2.1 Figure 16. Birds-eye-view of virtual environment routes A and B used for counterbalancing. Dashed line denotes correct route through maze. Red markers denote location of distal landmarks when route used for 'landmark' condition.

5.2.3. Design and procedure

All participants completed the BPVS-III and RCPM tasks before any other measures. Participants were then presented with either the LM or NLM condition VE maze (counterbalanced across participants in each group). A 'visual-matching' and 'landmark naming' task always immediately followed the LM condition for all participants.

5.2.3.1. 'Landmark' condition.

In the landmark maze (LM) condition, participants were asked to navigate from the starting position to find a "hidden exit" at the end of the maze (either layout A or B). Surrounding the maze were 12 distal landmarks (two distinct trees, two distinct lampposts, a playground, a cityscape, a high-rise building, a house, a traffic light, a red tower, a shop, and a block of flats), at least two of which were visible from each path. During the learning phase, participants were first shown the correct route by following a

grass path. On reaching the exit, a celebratory trumpet sound was played and the programme window automatically closed. The participant was then returned to the starting position, without the grass path, for the first learning trial. Here, participants were required to walk the route from memory. An error was counted if the participant travelled more than half way down an incorrect path. During the learning trials, the participant had to navigate through the correct route to the exit without error on two consecutive trials to reach learning criterion and move onto the test trial. Each participant was given a maximum of seven learning trials to reach criterion, unless zero errors were made on trial 7, then eight trials were given. As this was to check whether learning had occurred within 7 trials, if errors were made on trial eight, data from this trial were not included in the analysis.

Once the participant had learnt the route successfully (reached criterion) in the landmark condition, they were returned to the starting position of the maze, but this time with all landmarks removed. Participants were then asked to retrace the correct route to the exit. This single test trial was used to examine the extent to which participants continued to rely on the use of landmarks for successful navigation following learning, or whether they were able to use sequential egocentric coding to retrace the route.

5.2.3.2. 'No landmarks' condition.

As a control condition, to examine whether participants were able navigate through a maze that did not have any landmarks to begin with, participants were also asked to learn a route through the no-landmark maze (NLM).

Similar to the LM condition, participants were first shown the correct route by following a grass path to the hidden exit. Participants then entered the learning phase, without the grass path and were asked to navigate the correct route, without error. In line with LM condition learning trials, participants had to navigate the correct route with no errors on two consecutive trials (maximum seven trials, unless zero errors on trial 7, then 8 trials) to meet criterion.

5.2.3.3. ‘Visual matching’ task.

Immediately following the LM condition, participants were presented with a visual matching task, to examine the ability to remember the correct visual scenes from the maze. Participants were shown a series of images from the viewpoint of each of the six junctions of the maze that they had learned. For each trial, two images (one correct and one incorrect) were presented adjacent to each other on the computer screen. Participants were asked to select which of the two scenes they had actually viewed when walking through the maze. Incorrect scenes consisted of either an incorrect configuration (an incorrect spatial layout, but containing the correct landmarks), or included incorrect landmarks from different parts of the maze (but in the same configuration as the correctly presented scene). Each correct and incorrect scene pair was presented twice throughout the task (12 trials), with each image appearing once on the left- and once on the right-hand-side of the screen.

5.2.3.4. ‘Landmark naming’ task.

To examine whether participants were able to easily recognise and name each landmark, and therefore, to assess the saliency of each environmental marker as a potential navigational guide, a landmark naming task was used. Here, each of the twelve landmarks from the landmark-maze was presented individually on the screen and the participant was asked to name the object. Items were scored as correct if the correct name, a commonly used alternative, or synonym was given.

5.3 Results

5.3.1 Verbal and non-verbal abilities

To examine differences across groups on BPVS-III and RCPM scores, one-way analyses of variance (ANOVA) were conducted for both measures, with group (4 levels: 5 years, 7 years, 9 years, and WS) as a between-subjects factor. Similar to the findings

in studies 1 and 2, results demonstrated an uneven cognitive profile in WS, characteristic of the disorder (Jarrold et al., 1998; Martens et al., 2008), with nonverbal abilities significantly below TD 9 year-olds, and at a level no different from TD 5 and 7 year-olds, compared to relatively higher verbal abilities, significantly greater than TD 5 and 7 year-olds, but not significantly different from TD 9 year-olds (5.3.1.1 Table 12).

5.3.1.1 Table 12. Mean (SD) scores on BPVS-III and RCPM for each group

	Group				ANOVA		Post-hoc[a]
	WS (N=18)	5 years (N=16)	7 years (N=16)	9 years (N=16)	*F (df)*	*p*	
BPVS raw[b]	128.39 (15.38)	76.19 (6.78)	91.56 (12.85)	120.06 (11.26)	67.39 *(3, 65)*	*< .001*	5 < 7 < 9 = WS
BPVS stand[c]		92.94 (6.53)	88.25 (11.12)	90.00 (9.61)	1.04	*.361*	-
RCPM[d]	20.83 (6.21)	17.75 (2.54)	21.56 (3.97)	28.06 (4.11)	15.05 *(3, 65)*	*< .001*	WS = 5 = 7 < 9

[a] Tukey-corrected post-hoc tests, '=' refers to no significant difference at .05 level, and '<' denotes 'significantly less than' ($p < .01$); [b] BPVS-III: British Picture Vocabulary Scale-III raw scores; [c]BPVS-III standardised scores; [d]RCPM: Ravens Coloured Progressive Matrices (RCPM) raw scores

5.3.2. Learning phase

To examine route-learning abilities in both the 'with landmarks' (LM) maze condition and 'no-landmarks' (NLM) maze condition across groups, Mean number of learning trials taken to reach criterion (two consecutive trials without error) was calculated for each maze condition in each group. As a more sensitive measure of route-learning ability, the cumulative number of errors made across all learning trials

for each maze condition was also analysed. Descriptive statistics for these two dependent variables are displayed in 5.3.2.1 Table 12.

5.3.2.1 Table 13. Group Means (SD) for measures of performance on learning phase in Landmark (LM) and No-Landmark (NLM) mazes

		Group			
		WS (N = 18)	5 years (N = 16)	7 years (N = 16)	9 years (N = 16)
LM	Number of Learning Trials *(including two criterion trials)*	5.17 (1.89)	4.25 (1.84)	3.50 (1.16)	3.25 (1.44)
	Number of Errors	5.06 (4.35)	3.19 (3.47)	1.44 (1.26)	2.00 (2.19)
NLM	Number of Learning Trials *(including two criterion trials)*	7.00 (0.00)	5.75 (1.77)	5.94 (1.48)	5.50 (2.16)
	Number of Errors	15.94 (3.72)	9.06 (6.65)	7.94 (5.98)	7.81 (6.48)

5.3.2.2. Number of learning trials to reach criterion.

Data from the LM condition were normally distributed for TD 5 and 7 year-olds (Kolmogorov-Smirnov, $p > .05$), but not for the TD 9 year-olds or WS group. Given that half of the groups presented with normally distributed data, and that ANOVA is robust to violations of normality (Field, 2009), parametric analyses were conducted. Data were not normally distributed for any group for 'number of learning trials' in the NLM condition (Kolmogorov-Smirnov, $p < .01$ for all). Also, as none of the WS participants (and the majority of TD participants) failed to meet learning criterion for the NLM, and thus reached the maximum trial limit, non-parametric analyses were conducted on this data and analysed separately from LM data.

Results of a one-way ANOVA (with Tukey-corrected pairwise comparisons) for number of learning trials on the LM maze (including the two correct criterion trials), showed a significant effect of group, $F(3, 65) = 4.85$, $p = .004$, $\eta^2 = .19$. This was due to the WS group requiring a significantly greater number of trials to learn the route than TD 7 year-olds and 9 year-olds; $p = .020$ and $p = .006$, respectively. No significant differences were found between WS and TD 5 year-olds ($p = .360$), or between any TD groups ($p > .05$ for all). A non-parametric equivalent of this analysis was conducted, with comparable results.

For the NLM, results of a non-parametric Kruskal-Wallis test yielded a significant effect of group on number of learning trials, $H(3) = 8.43$, $p = .038$. Post-hoc Mann-Whitney tests showed that this was due to the WS group requiring a significantly greater number of trials than TD 5 year-olds ($U = 90.00$, $z = -2.81$, $p = .005$, $r = -.48$), TD 7 year-olds ($U = 81.00$, $z = -3.08$, $p = .002$, $r = -.53$), and TD 9 year-olds ($U = 90.00$, $z = -2.32$, $p = .021$, $r = -.39$). No significant differences were found between any TD groups ($p > .05$ for all).

5.3.2.3. Number of errors across learning trials.

5.3.2.3.1. Errors made at each junction.

To examine the pattern of performance during learning of the 6-turn routes, Mean number of errors made at each junction across all learning trials was calculated for each group. Mean number of errors at each junction for all groups on LM and NLM are displayed in 5.3.2.3.2 Figure 17.

Data from the LM were normally distributed (Kolmogorov-Smirnov, $p > .05$) for WS and 5-year-old groups, but not for 7 and 9 year-olds. Data from the NLM were normally distributed for all groups. Given that the data were normally distributed for the majority of groups across the two maze conditions and ANOVA is robust to violations of normality (Field, 2009), results of parametric analyses are reported. Non-parametric analyses were conducted on LM maze, with comparable results.

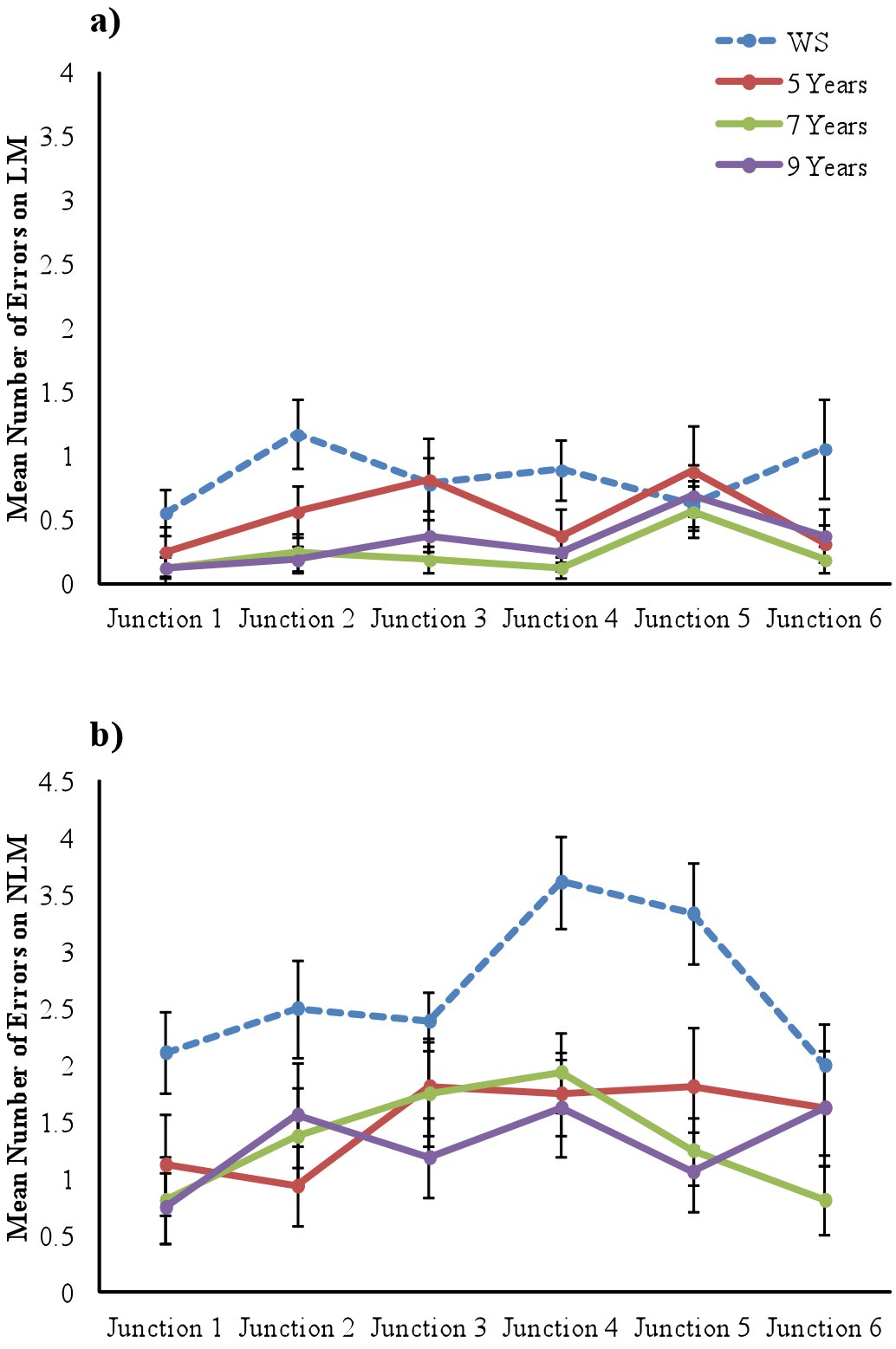
Firstly, to examine the effects of counterbalancing on mean number of errors, separate mixed ANOVAs with between-participant factor of groups (4 levels: 5, 7, 9 and WS) and within-participant factors of 'maze' (2 levels: LM and NLM) included either a between-participant factor of 'maze-order' (2 levels; order 1: LM before NLM; order 2: NLM before LM)' or 'route-order' (2 levels: A first; B first)'. Given that no significant main effects were found for either 'maze-order' ($F(1, 58) = .29$, $p = .592$) or 'route-order' ($F(1, 58) = .15$, $p = .699$), nor were there any significant interactions with either variable ($p > .05$ for all) it was concluded that there were no order effects, and so these variables were not included in subsequent analyses that examined error patterns across junctions or error types.

A mixed ANOVA with between-participants factor of 'group' (4 levels: 5, 7, 9 and WS) and two within-participant factors of 'maze' (2 levels: LM and NLM) and 'junction' (6 levels: 1–6) was conducted. There was a significant main effect of Group, $F(3, 62) = 10.77$, $p < .001$, partial $\eta^2 = .34$, with Tukey-corrected pairwise comparisons showing that this was due to significantly greater number of errors in the WS group than any TD group ($p < .01$ for all). No significant differences were found between any TD groups. There was also a significant main effect of Maze, $F(1, 62) = 89.93$, $p < .001$, partial $\eta^2 = .59$, due to more errors made during learning of the NLM than the LM maze. A main effect of Junction was also found, $F(5, 310) = 4.80$, $p < .001$, partial $\eta^2 = .07$. This is explored for each maze separately in light of the maze by junction interaction discussed below.

Results also showed a significant maze by junction interaction, $F(5, 310) = 2.55$, $p = .028$, partial $\eta^2 = .04$, and a near-significant maze by group interaction, $F(3, 62) = 2.67$, $p = .055$, partial $\eta^2 = .11$, showing that there were different patterns of performance for each of the two maze conditions. However, no junction by group interaction, $F(15, 310) = .89$, $p = .566$, nor maze-by-junction-by-group interaction was found, $F(15, 310) = 1.53$, $p = .094$, indicating that this different pattern of performance across junctions between the two maze conditions did not differ across groups. To further examine the interactions with maze, each maze was analysed separately.

For errors across junctions in the LM condition, a mixed ANOVA showed a significant main effect of Group, $F(3, 62) = 4.56$, $p = .006$, partial $\eta^2 = .18$, with Tukey-corrected pairwise comparisons showing this was due to the WS group making significantly greater number of errors than TD 7 and 9 year-olds ($p = .006$ and $p = .028$, respectively). No significant difference was found between WS and TD 5 year-olds ($p = .306$), or between any TD groups ($p > .05$ for all). A significant within-participant effect of Junction was also found, $F(4.52, 280.23) = 2.36$, $p = .046$, partial $\eta^2 = .05$. Post-hoc comparisons found that this was due to significantly fewer number of errors at junction 1 compared with junctions 2 ($p = .031$), 3 ($p = .026$) and 5 ($p = .004$).

Results for the NLM condition also showed a significant main effect of Group, $F(3, 62) = 7.87$, $p < .001$, partial $\eta^2 = .28$. Here however, Tukey-corrected pairwise comparisons showed that the WS group made significantly greater number of errors than all TD groups on this maze ($p < .01$ for all). This was different to performance in the LM condition, in which the WS group performed in line with TD 5 year-olds, and thus explains the marginal maze by group interaction. No significant differences were found across TD groups ($p > .05$ for all). A significant within-participant effect of Junction was also found, $F(5, 310) = 4.01$, $p = .002$, partial $\eta^2 = .06$. Post-hoc comparisons showed that this was due to significantly fewer number of errors at junction 1 than junctions 3, 4 and 5 ($p = .014$, $p < .001$, and $p = .012$, respectively), and significantly greater number of errors at junction 4 than at junctions 2 and 6 ($p = .018$ and $p = .004$, respectively). This pattern of errors therefore differed to that seen in the LM, and thus explains the maze by junction interaction, as learning in the NLM led to more errors in the middle of the maze than at any other point.



5.3.2.3.2 Figure 17. Mean (SE) number of errors made at each junction across learning trials on a) Landmark Maze and b) No-Landmark Maze conditions for each group

5.3.2.3.3. Types of errors made during learning.

As a further investigation into errors made during the learning trials for each maze condition, errors were separated into three categories, in line with the method used by Farran, Courbois, Van Herwegen, and Blades (2012), and included as a within-participants factor in the analyses. Errors were coded as a) 'single errors' (an error that occurred only once at a specific junction across all learning trials), b) 'consolidation errors' (errors that occurred at the same junction on more than one learning trial, but not on consecutive trials), or c) 'perseveration errors' (errors that occurred at the same junction on two or more consecutive learning trials). Mean number of each type of error made during the LM and NLM conditions are displayed in 5.3.2.3.4 Figure 18.

For all error types in each group (except single errors in 5 year-olds, $p = .101$), data were not normally distributed (Kolmogorov-Smirnov, $p = < .05$). However, given that ANOVA is robust to violations of normality (Field, 2009), parametric analyses were conducted on the data. Equivalent non-parametric analyses were also conducted, with comparable results for all main effects, and are therefore not reported. A mixed ANOVA with between-participants factor of 'Group' (4 levels: 5, 7, 9 and WS) and two within-participant factors of 'Maze' (2 levels: landmark and no-landmark) and 'Error Type' (3 levels: single, consolidation, and perseverative) was conducted. Significant main effects of Group and Maze, and Group by Maze interaction are not reported as these were as detailed above (see section 5.3.2.3.1). Results also found a significant main effect of Error Type, $F (1.43, 88.59) = 44.72$, $p < .001$, partial $\eta^2 = .42$, with pairwise comparisons indicating a significant difference across all error types ($p < .001$ for all).

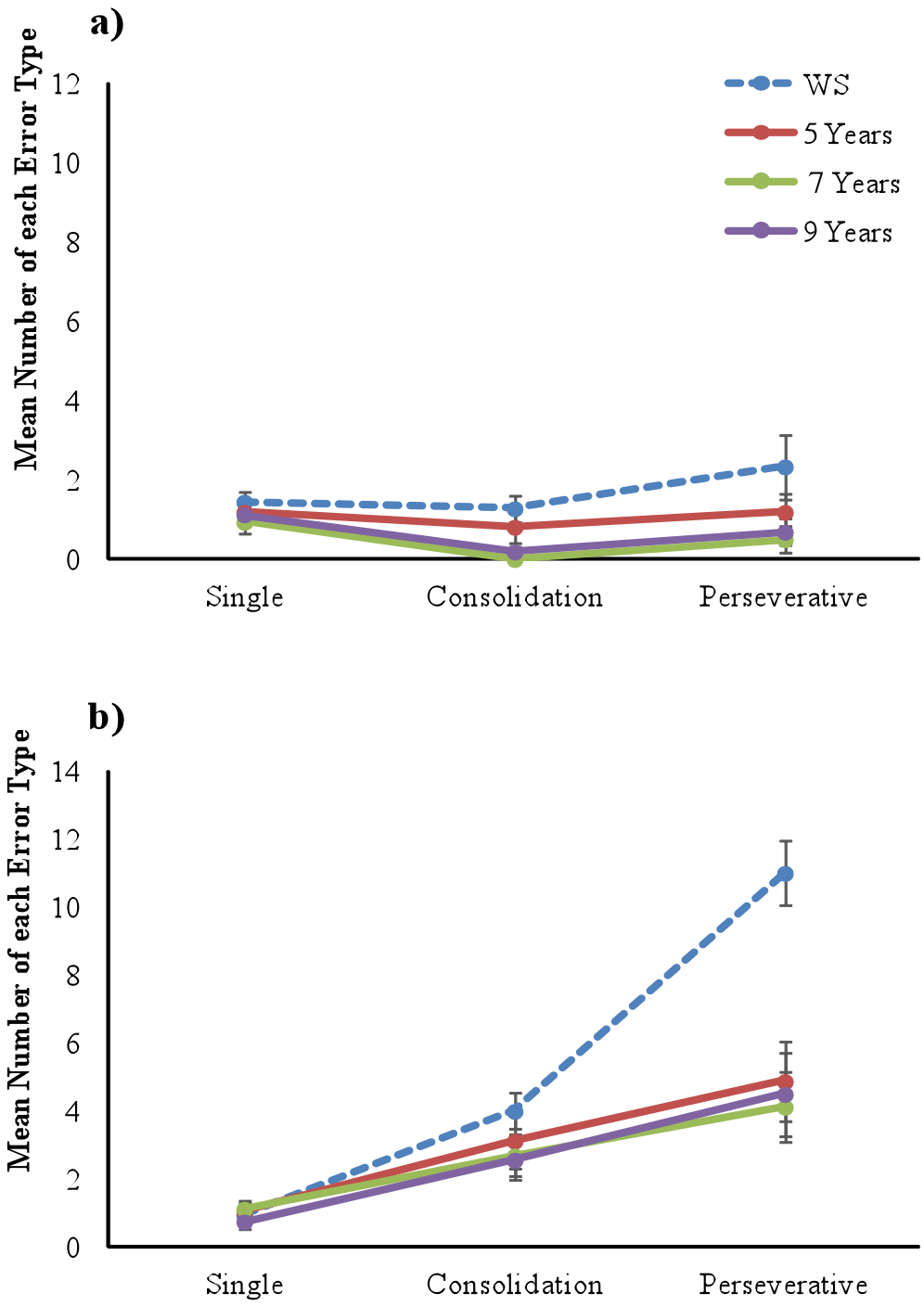
Results also showed a significant Maze by Error-Type interaction, $F (1.87, 115.94) = 46.22$, $p < .001$, partial $\eta^2 = .43$, and significant Error-Type by Group interaction, $F (4.29, 88.59) = 6.99$, $p < .001$, partial $\eta^2 = .25$. A significant 3-way Maze by Error Type by Group interaction was also found, $F (5.21, 107.74) = 3.98$, $p = .002$, partial $\eta^2 = .16$, showing that there was a different pattern of errors seen between the two mazes, that differed across groups. Given the significant main effects, significant

interactions, and difference in number of trials to reach criterion, each maze was analysed separately (main effects of 'Group' are not reported as these are as reported in section 5.3.2.3.1.).

Results from the analysis of types of errors made in the LM condition learning trials, found a significant main effect of 'Error Type', $F(1.45, 89.82) = 4.25$, $p = .028$, partial $\eta^2 = .06$. Pairwise comparisons found that this was due to significantly fewer consolidation errors than single or perseverative errors ($p = .003$ for both). However, no significant Error-Type by Group interaction was found, $F(4.35, 89.82) = .967$, $p = .967$, showing that the pattern of errors observed in the LM did not differ across groups.

Results from the analysis of error type in the NLM condition learning trials, also found a significant main effect of 'Error-Type', $F(1.75, 106.41) = 55.18$, $p < .001$, partial $\eta^2 = .47$. Pairwise comparisons found that this was due to a significant difference across all error types ($p < .001$ for all). In addition, a significant Error-Type by Group interaction was found, $F(5.15, 106.41) = 6.64$, $p < .001$, partial $\eta^2 = .24$.

To examine this interaction further, error type was examined separately across groups. Results of a one-way ANOVA revealed a significant difference only in Mean number of perseverative errors across groups, $F(3, 65) = 9.49$, $p < .001$. Tukey-corrected pairwise comparisons showed that this was due to a significantly greater number of perseverative errors made by the WS group than any TD groups ($p \leq .001$ for all). No significant differences across TD groups were found ($p > .05$ for all).

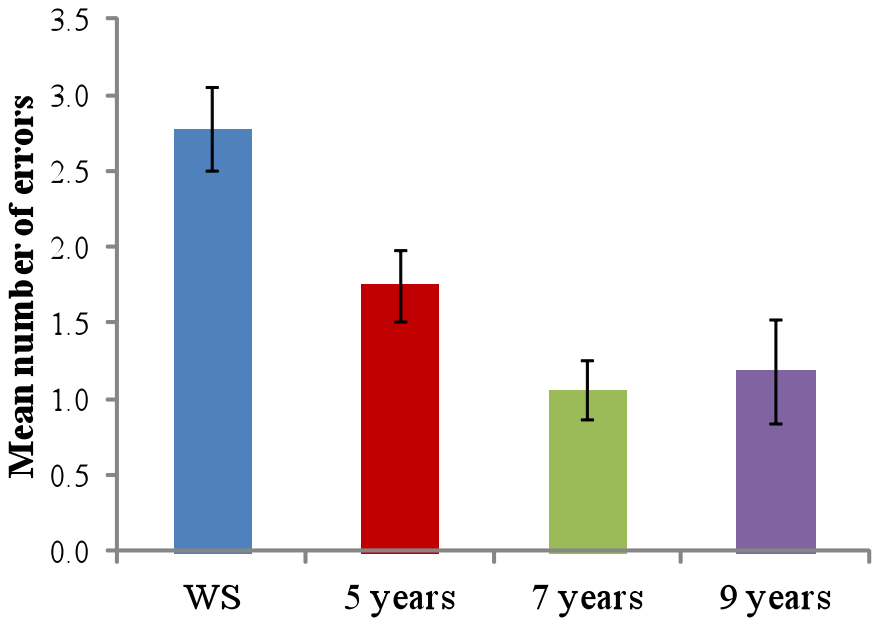


5.3.2.3.4 Figure 18. Mean (SE) number of each error type made across learning trials on a) Landmark Maze and b) No-Landmark Maze conditions for each group

5.3.3. 'Landmarks-removed' test trial

As a measure of the ability to use a sequential egocentric strategy following learning in the landmark-condition, participants were asked to immediately complete

the route one final time, with all landmarks removed. Mean number of errors made during the test trial was calculated for each group (see 5.3.3.1 Figure 19). Data were normally distributed (Kolmogorov-Smirnov, $p > .05$) for 7 and 9 year-olds, but not for WS and 5-year-olds. However, given that half of the data were normally distributed, parametric one-way ANOVA was conducted to examine the mean number of errors made across groups. Results yielded a significant difference across groups, $F(3, 65) = 8.89$, $p < .001$, with Tukey-corrected pairwise comparisons showing that the WS group made a significantly greater number of errors than all TD groups (5 years, $p = .038$, 7 years, $p < .001$, 9 years, $p < .001$). No significant differences were found across TD groups ($p > .05$ for all).

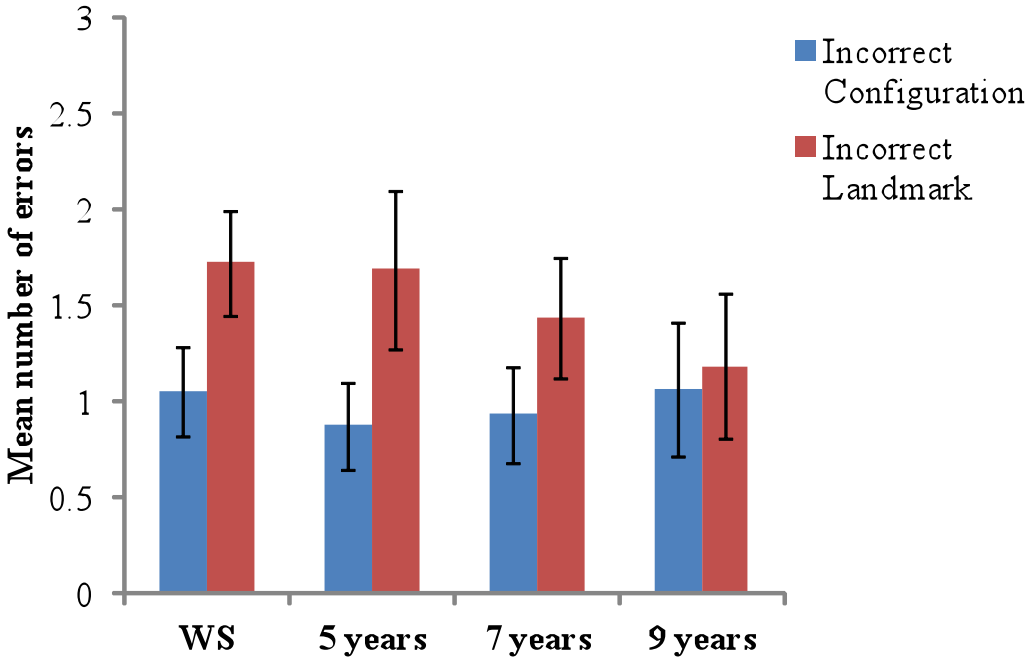


5.3.3.1 Figure 19. Mean (SE) number of errors made during 'landmarks removed' test trial for each group

5.3.4. 'Visual-matching' task

Incorrect scenes on the visual matching task were separated into those with an incorrect configuration (but with correct landmarks for that junction) and those that included incorrect landmarks (but in the correct configuration for that junction). Mean

number of errors (incorrect scene choices made, out of 12 trials) were calculated for each group. Data were normally distributed (Kolmogorov-Smirnov, $p > .05$) for all groups, except 9 year-olds ($p = .014$), and therefore compared using a 2-way ANOVA with a between-participant factor of group (4 levels: WS, 5, 7 and 9 years) and within-participant factor of 'scene type' (2 levels: incorrect configuration and incorrect landmark). Although significantly below ceiling (using one-sample t-tests), all groups performed well on this task, with few errors made (5 years: M= 9.44 (1.67), $t(15) = -6.13$, $p < .001$; 7 years: M= 9.63 (1.67), $t(15) = -5.69$, $p < .001$; 10 years: M= 9.75 (2.69), $t(15) = -3.34$, $p = .004$; WS: M= 9.22 (1.89), $t(17) = -6.22$, $p < .001$). No significant differences were identified across groups, $F(3, 62) = .22$, $p = .882$, indicating proficient ability to visually match correct scenes from a recently-learned maze in all groups (see 5.3.4.1 Figure 20 for Mean errors in each group). However, a significant effect of scene type was found, $F(1, 62) = 8.17$, $p = .006$, partial $\eta^2 = .12$, with pairwise comparisons indicating that participants made significantly more errors when the incorrect visual scene contained an incorrect landmark compared to an incorrect configuration ($p = .006$).



5.3.4.1 Figure 20. Mean (SE) number of errors (incorrect scenes chosen) on 'visual-matching' task in each group. Incorrect scenes are separated into those that included an 'incorrect configuration' and those with an 'incorrect landmark'

5.3.5. Landmark naming task

As a test of the saliency of each environmental feature used in the landmark condition maze, the number of correct or appropriate labels given for each of the 12 landmarks was calculated for each group. Data significantly deviated from normal for each group (Kolmogorov-Smirnov, $p < .05$), and so non-parametric analyses are reported. Results indicate that the landmarks were easily named, with a high number of correct labels given by each group [Mean (SD)]; WS: 11.83 (.38), 5 years: 11.50 (.82), 7 years: 11.69 (.60), 9 years: 11.94 (.25), with no significant differences found across groups, H (3) = 4.07, $p = .254$.

5.4 Discussion

The present study examined the extent to which individuals with WS rely on the presence of landmarks both for learning and for recalling a route, compared to TD

children aged 5-9 years. On learning a six-turn route in a VE maze with 12 distal landmarks, individuals with WS performed in line with TD 5 year-olds, although required a significantly greater number of trials and made more errors than TD children aged 7 and 9 years. This finding is in line with that of previous route-learning studies in WS, showing route-learning performance at a level expected based on non-verbal reasoning ability (Farran et al., 2010; Farran, Courbois, Van Herwegen, & Blades, 2012). On learning trials in a maze without landmarks (NLM) however, individuals with WS presented with a significantly higher level of impairment than all TD groups, with none of the participants in the WS group successfully able to learn the route. As such, although all groups demonstrated substantially poorer performance on learning a maze without landmarks compared to one with landmarks, the negative impact on learning without visual cues for navigation was seen to a greater extent in individuals with WS. This difficulty in way-finding without the presence of visual cues was further substantiated when landmarks were removed following learning in the LM. Here, even having successfully learnt the route with landmarks to a level comparable with TD 5 year-olds, individuals with WS made reliably more errors than all TD groups once these were removed, demonstrating a greater reliance on the presence of visual markers to guide learning and subsequent repetition of a series of decision points along a route.

No significant differences were found in performance across the three TD groups on measures of route-learning in either maze condition, or on number of errors made following the removal of landmarks. This absence of a developmental difference on these tasks is indicative of, not only a high level of route-learning ability by 5 years of age, but also the capacity to fall back on the use of a sequential egocentric navigation strategy when required from at least 5 years. This is, in part, counter to earlier findings of age-related changes in a reliance on landmarks to make correct turns at decision points along a newly-learnt route (e.g., Cohen & Schuepfer, 1980; Jansen-Osmann & Wiedenbauer, 2004). The use of proximal landmarks in the above-mentioned studies, compared to the use of distal landmarks in the present study may underlie these different findings, particularly given that distal (global) landmarks may have allowed

participants to develop a single, integrated representation of the route (Ruddle et al., 2011), resulting in less reliance on landmarks, even in the youngest group. Alternatively, given that the age range in the present study did not extend as high as in previous studies, this may have resulted in these contradictory findings, where the addition of an older TD group here may have yielded improvements with age. That said, the present results are in line with findings that young children use landmark information to enhance way-finding to the same extent as older children and adults (Jansen-Osmann & Fuchs, 2006). In addition, the present findings alongside those from study 2 and findings by Bullens, Iglói, et al. (2010) suggest that the use of sequential egocentric coding is a viable navigation strategy that can be utilised by children as young as 5 years of age. This is akin to the spontaneous navigation strategy predominantly employed by typical adults on comparable route-learning tasks (Iglói et al., 2009).

The high level of ability to successfully retrace a route observed in TD children following the removal of landmarks begs the question of whether participants in these groups were simply remembering a verbal sequence of left-right turns to complete the route, and were thus unfazed by the change in environmental appearance. There are three arguments to counter this. First, children aged 5 years have difficulty in the use and representation of 'left/right' spatial terms (Landau & Hoffman, 2005) and so successful execution of this strategy would have been particularly problematic in this group. Second, errors (albeit very few) were observed following landmark removal in all TD groups, indicating the role of landmarks at some level in supporting the development of spatial knowledge in these groups. Third, all TD groups performed highly on the visual-matching task, demonstrating that they had attended to and encoded this information for use in way-finding, a process that would not be necessary had they solely relied upon verbally labelling the left-right sequence. It can be inferred therefore that during learning in TD children, but not in individuals with WS, a sequential egocentric representation of the temporal order of bodily turns was developed

simultaneously to the paired-associative learning of directional responses to specific landmarks.

The use of a sequential egocentric strategy in which the temporal sequence of body turns is encoded, requires cognitive demands corresponding to those required for episodic or procedural memory (Iglói et al., 2009; Packard & McGaugh, 1996), and is associated with activation in the left hippocampus (Iglói et al., 2010). Given the known cortical atrophy associated with WS that includes the hippocampus (Meyer-Lindenberg et al., 2005), it stands to reason that spatial encoding that is typically supported by these neural networks would be impaired in this disorder. Indeed, structural and functional abnormalities in the hippocampal region in WS are likely associated with not only impairments in the use of an allocentric spatial frame of reference in WS (study 2), but also with difficulties in the use of a sequential egocentric representation, as identified in this study.

Further insight into the nature of impairments in the use of a sequential egocentric strategy in WS was attained by examining the categorisation and pattern of errors throughout learning. In both maze conditions, although particularly in the NLM, the pattern of errors across junctions was that of a 'primacy-recency effect' serial position curve, with turns at junctions in the centre of the maze more difficult to learn than those at the beginning or end. A pervasive phenomenon of human memory (R. C. Atkinson & Shiffrin, 1968; Murdock, 1962), this primacy-recency effect is also seen for spatial episodic memory events in rodents using large-scale maze paradigms (Bolhuis & van Kampen, 1988; Kesner, Measom, Forsman, & Holbrook, 1984). However, a recency effect (for instance with significantly fewer errors made at junction 6 than at 4) on the maze that did not contain visual cues to support recognition memory (NLM), indicates that participants must have encoded some metric information about this environment to track how far through the maze they had travelled, in order to know that they were nearing the final junction. This pattern was also seen in WS, and was particularly unexpected given our understanding of deficits in spatial knowledge in this group. An alternative explanation is that these results may have arisen from the use of

non-spatial strategies such as a counting technique to keep track of when the final junction was approaching. However, given that none of the participants in the WS group were able to reach learning criterion on the NLM, this is indicative of considerable impairments in spatial knowledge. This was particularly evident in difficulties learning from previous junction errors when no landmarks were present to aid decision making on subsequent trials.

This particular difficulty in WS in learning a 6-turn sequence of turns was further reflected in the high number of perseverative errors in this group, compared to other error types and to performance by all TD groups. At a behavioural level, perseverative errors have been previously noted in WS during navigation tasks (Farran, Courbois, Van Herwegen, & Blades, 2012; Mandolesi et al., 2009). This is indicative of difficulties inhibiting previous incorrect responses and is supported by findings that individuals with WS fail to engage cortical and subcortical structures in the frontostriatal regions that mediate response inhibition (Mobbs et al., 2007). In the current study, however, a significantly greater number of perseverative errors in WS compared to TD groups was not identified during learning in a maze with landmarks. This difference may simply reflect the natural outcome of the scoring criteria when a high total number of errors are made (e.g., during the NLM). Alternatively, the presence of visual cues in the LM condition may have supported the formation of cognitive representations of landmarks to guide way-finding in the WS group, leading to fewer perseverative errors. However, a high number of perseverative errors in WS were found by Farran and colleagues (2012) on a maze that contained landmarks. As such, the use of proximal landmarks in the Farran et al. study and the use of distal landmarks in the present study may provide the crucial comparison for future research.

The substantial impairments in WS on tasks that required sequential egocentric coding suggest that individuals with this disorder instead rely on the presence of landmarks to navigate, and to a greater extent even than TD children of comparable non-verbal ability. Successful utilisation of landmarks for way-finding on a previously traversed route requires storage of visual information at decision points, even if the

sequential order of these choice points are not encoded. As such, if individuals with WS rely on the use of a visual-matching strategy to navigate, it is reasonable to surmise that they would score highly on tests of scene recognition. This hypothesis was supported in the current study, showing that participants in this group were successful at identifying correct visual scenes from the maze with landmarks. This is in line with findings from an individual with bilateral hippocampal damage who presented with spatial impairments in allocentric and context-dependent episodic memory, but was able to recognise scenes from a VE environment, suggesting that visual pattern-matching is not associated with the hippocampus (Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001). Previous research in WS has also shown that some perceptual abilities may be relatively unimpaired. For instance, although individuals with WS are typically impaired on block construction tasks (e.g., Bellugi et al., 1988), performance on perceptual components of similar tasks are found to be at the level of mental-age matched controls (Deruelle et al., 2006; Rondan, Mancini, Livet, & Deruelle, 2003).

On the visual matching task, the finding that incorrect-landmark scenes were more difficult to determine than incorrect-configuration scenes was not anticipated; an outcome that was particularly unexpected in WS, given the known difficulties with coding configurational information in this group (e.g., Bernardino et al., 2013; Nardini et al., 2008). However, this distinction may have been related to differences in the ability to detect changes in fine and coarse visual information. For instance, in the incorrect-landmark scenes, the general outline of the scene would have been similar to the correct layout, making it more difficult to disambiguate between correct and incorrect choices than with changes to coarse information, as seen in incorrect-configuration scenes. However, it is difficult to make robust conclusions from this task, particularly given that in some scenes more landmarks were visible than in others, meaning that scenes were not matched for level of difficulty. Indeed, the pattern of performance was the same across TD and WS groups, suggesting that this outcome was more related to the specific nature of the task than a reflection of a syndrome-specific pattern of performance. An alternative method for future studies using such visual-

matching tasks should therefore include an incorrect-landmark and incorrect-configuration version of each scene for comparison. That said, it is important to note the high level of accuracy in all TD groups and the WS group on both scene-types, indicating that all groups were able to use the visual information from the environment to guide way-finding by some means.

5.5 Conclusions

These findings indicate that individuals with WS rely on visual landmarks for route-learning and way-finding, to a greater extent than TD children of comparable non-verbal ability. All participants with WS failed to learn a route that did not contain landmarks, which required the development of a representation of the temporal sequence of body turns. When learning a route with landmarks, TD children, but not individuals with WS, were able to simultaneously develop a sequential egocentric representation of the route to aid way-finding in situations such as when landmarks were removed. Individuals with WS instead relied on a visual matching strategy by which to navigate, which is susceptible to errors following changes to the physical presentation of the environment (i.e. the removal of landmarks). Impairments in memory processes involved in episodic spatial events such as remembering the sequence of bodily rotations through a route is in line with atypical development in associated cortical regions in WS. These findings provide insight, not only into the impairments in WS in large-scale spatial cognition, but into the strategies that may be commonly employed by individuals with this disorder to support wayfinding, when typical strategies and egocentric and allocentric spatial frames of reference are not available to them.

Chapter 6

Study 5: The contribution of gene expression to the Williams syndrome visuospatial phenotype: Insights from individuals with partial deletions

6.1 Introduction

The studies presented in the previous chapters have examined small- and large-scale visuospatial impairments in WS at the behavioural level. These studies have demonstrated a diverse range of deficits within this domain in WS. However, to fully understand the complex phenotypic presentation of WS, it may be important to elucidate the role of the deleted genes within the WS critical region (WSCR) of chromosome 7. The study in the present chapter provides an examination of the genetic contribution to the WS cognitive profile. Here, an in-depth profiling of the visuospatial domain in two individuals with different genetic deletions on the WSCR highlights the importance of taking a multi-level approach to understanding visuospatial cognition and the phenotypic variability in this disorder.

The deleted region on chromosome 7q11.23 in Williams Syndrome (WS) typically spans some 1.55 to 1.84 megabase pairs (Mb) of contiguous genomic DNA (Antonell et al., 2010; Bayés et al., 2003; Pober, 2010; Tassabehji et al., 1999). The common deletion size of ~1.55 Mb (in approximately 95% of WS cases) stems from a recombination between the centromeric and medial low-copy-repeat (LCR) sequence blocks B, which flank the (~1.2 Mb) single copy gene region, and the less frequent deletion of ~1.84 Mb (in about 5% of WS cases) arises from a recombination between the centromeric and medial LCR block A copies (Koehler et al., 2014; X. Meng et al., 1998; Peoples et al., 2000; Schubert, 2009); see 6.2.1.1 Figure 21.

Twenty-seven to twenty-eight coding genes have been mapped within the typical WSCR, and consist of the 22 single copy region genes and up to six genes within the flanking medial LCR blocks C and B, depending on the breakpoint location (Koehler et al., 2014; Merla, Ucla, Guipponi, & Reymond, 2002; Schubert, 2009). The

contribution of individual genes to the WS phenotype, however, remains elusive. Thus far, unequivocal genotype-phenotype correlation has only been established for one gene; with haploinsufficiency for the elastin gene (*ELN*) being associated with arterial stenoses (Ewart et al., 1994; Li et al., 1997; Osborne, 2012; Pober, 2010).

Animal knock-out models have provided some advancement of the delineation of which genes contribute to the WS phenotype. The deleted band on human chromosome 7q11.23 has an orthologous region in mouse chromosome 5G1-G2 (Valero, de Luis, Cruces, & Perez Jurado, 2000), in the same sequential order, although inverted. However, whilst being a good model for this reason, there are shortcomings in generalising animal models to human cognition, including possible differences in regulatory effects and patterns of expression of these genes, particularly over development (Osborne, 2010, 2012). In addition, measurable mouse behaviours are not likely to always be directly comparable to cognitive expression in humans. As such, examination of cognitive functioning in individuals with atypical rearrangements of genes on 7q11.23 offers a favourable and appropriate alternative.

A number of individuals with atypical deletions within the WSCR on chromosome 7 have been reported (e.g., Karmiloff-Smith, Grant, et al., 2003; C.A. Morris et al., 2003), and provide insight into the contribution of specific genes to the phenotypic outcome of WS. Previous research into individuals with partial deletions has sought to identify candidate genes responsible for deficits in domains such as global intelligence (C.A. Morris et al., 2003), social cognition (Karmiloff-Smith et al., 2012), and spatial cognition (Frangiskakis et al., 1996; Gray, Karmiloff-Smith, Funnell, & Tassabehji, 2006; Smith et al., 2009). It is often reported that the more severe phenotypic outcomes occur with deletions encompassing the region telomeric to the *ELN* gene compared to more centromeric deletions (e.g., Frangiskakis et al., 1996; Heller, Rauch, Lüttgen, Schröder, & Winterpacht, 2003); thus denoting a specific role of the distal genes in the development of WS cognitive features.

In relation to spatial cognition, one study that examined two families with a partial WS phenotype, including supravalvular aortic stenosis (SVAS) and deficits in

visuospatial construction, found that affected family members were hemizygous for *ELN* and LIM domain kinase 1 (*LIMK1*) WSCR genes (Frangiskakis et al., 1996). Given that *ELN* is not expressed in the brain and mutations of which are not associated with spatial deficits but with cardiovascular abnormalities, it was concluded that it must be the other deleted gene, *LIMK1*, that plays an important role in the phenotypic expression of impaired spatial cognition in WS. Indeed, in vivo, *Limk1* knockout mice have impaired spatial learning performance when tested on reversal learning in the Morris water maze (Y. Meng et al., 2002). They also present with abnormal synaptic structure and neuronal spine morphology, as well as altered hippocampal long-term potentiation.

The role of *LIMK1*, however, has remained inconclusive, with other studies of patients with partial deletions that include *LIMK1* suggesting that hemizygosity for this gene does not in itself result in deficits in visuospatial cognition (e.g., Gray et al., 2006; Tassabehji et al., 1999). Using a large battery of perceptual and visuospatial tasks, Gray and colleagues (2006) report a detailed assessment of two patients with deletions of only *ELN* and *LIMK1*, compared with two adults with full WS matched on verbal ability. A profile of normal spatial performance emerged from the two partial deletion patients compared to those with the full deletion, suggesting that *LIMK1* alone does not account for the WS spatial phenotype. In addition, the successful performance of these same two partial deletion patients on a large-scale spatial task indicated that the hemizygotic deletion of *LIMK1* was also insufficient to result in the poor large-scale search strategies identified in individuals with full WS on the same task (Smith et al., 2009).

These findings concur to indicate that the sole deletion of *LIMK1* is not sufficient to result in deficits in any form of spatial cognition. Instead, the authors suggest that *LIMK1* may play a role in the spatial cognitive profile in WS only when hemizygously deleted alongside other genes, particularly those at the telomeric end of the WSCR. It is these latter genes that have been the focus of recent studies.

Hirota et al. (2003) present a detailed analysis of the relationships between partial deletions in three patients and their performance on standardised psychometric

tests. The authors suggest that the general transcription factor (GTF) genes *GTF2I* and *GTF2IRD1*, at the telomeric end of the WSCR, are likely to play a disproportionate and crucial role in the development of neural pathways involved in visuospatial cognition. Similarly, clinical-molecular correlations in partial 7q11.23 patients by Antonell et al. (2010), suggest that functional hemizygosity for *GTF2I* and *GTF2IRD1* likely contribute to the craniofacial phenotype, intellectual deficit and visuospatial constructive difficulties associated with WS. However, *GTF2IRD1* alone was also not found to be sufficient to result in a visuospatial deficit.

Dai et al. (2009) also sought to delineate the role of these transcription factors in the WS phenotype, finding that an individual with an atypical deletion that included *GTF2IRD1*, but not *GTF2I*, presented with poor performance on a number of spatial subtests from the Wechsler Preschool and Primary Scale of Intelligence- Revised (WPPSI-R) (Wechsler, 1989), including 'Block Design', 'Object Assembly', and 'Mazes'. Preservation of the normal copy number of *GTF2I* in this individual was argued to contribute to the relative strengths found in those non-verbal cognitive measures that did not require visual-motor integration ('Picture Completion' and 'Geometric Design Recognition'), and in verbal cognition. This provides further support that the GTF-family genes at the telomeric end of the WSCR are likely to make a significant contribution to the WS visuospatial phenotype.

The GTF genes are also thought to have widespread effects on the expression of other genes (Young et al., 2008), and are differentially expressed in the developing brain compared to the adult brain (Osborne, 2012). The impact of mutations of these telomeric genes, particularly on the expression of other genes, may therefore be diverse and have varying cascading effects throughout development. As such, to gain a more thorough understanding of the role, combinatorial effects, and penetrance of all coding genes within the WSCR (particularly the GTF genes) on the phenotypic profile of WS, research must examine the different effects of specific genetic mutations across partial deletion patients with differing genomic makeup.

It is not only at the level of the genotype that more in-depth research has been necessary; the phenotypic outcome also requires more subtle analyses rather than solely relying on psychometric spatial tasks. Studies 1 and 2 in this thesis sought to elucidate whether there are dissociable deficits within the visuospatial domain in individuals with the full WS deletion, using a variety of tasks at different spatial scales. In line with previous reports of impaired visuospatial abilities in individuals with full WS (e.g., Farran et al., 2010; Farran & Jarrold, 2003; Fayasse & Thibaut, 2003; Jarrold et al., 1998; Nardini et al., 2008; Pani et al., 1999), the findings thus far highlight the multifaceted nature of spatial cognitive difficulties associated with this disorder. Indeed, both small- and large-scale spatial abilities are compromised, although not necessarily to equal extent. However, the specific genes or gene combinations that contribute to these small-scale and large-scale spatial impairments remains a matter to be addressed. Attempts to examine the genotypic correlations with these specific spatial deficits must therefore also address the use of these different cognitive processes in individuals with partial deletions within the WSCR.

Previous measures of spatial cognition in individuals with partial genetic deletions have, for the most part, relied on the use of psychometric tasks, or small-scale (albeit hypothesis-driven) neuropsychological tasks. For this reason, it is imperative to also examine performance on the same novel, hypothesis-driven small-scale tasks and navigational large-scale tasks used in individuals with the full WS deletion, which tap into egocentric and allocentric spatial cognitive demands.

The current chapter presents case studies of the spatial cognitive profiles of two individuals (HR and JB) with contrasting partial genetic deletions within the WSCR. Neither participant meets both genotypic and phenotypic criteria for full WS, although both are seen to present with an atypical cognitive profile. Previous comparisons of social cognition in these two patients (Karmiloff-Smith et al., 2012), highlight the different levels of social impairment that result from such contrasting deletions.

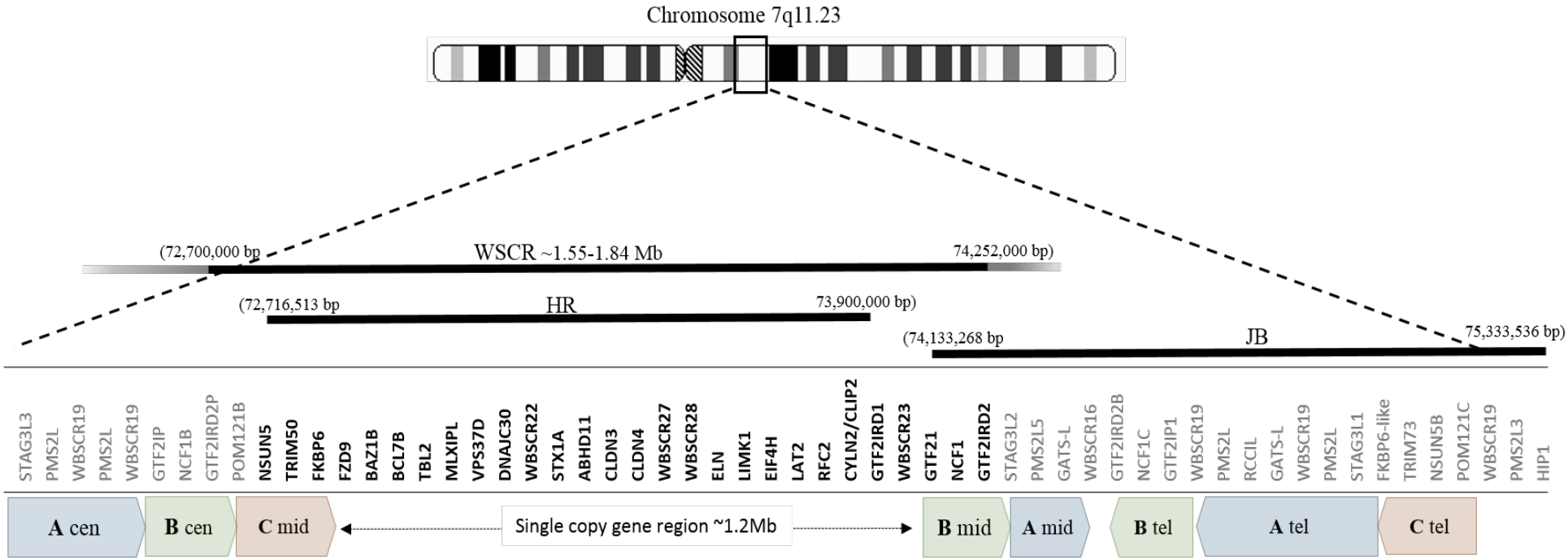
The impact of these differing genetic deletions in the WSCR on visuospatial cognition was examined in this chapter by investigating performance of HR and JB on

the same range of small- and large-scale spatial tasks presented in studies 1 and 2, and compared to performance on the same tasks in typically developing (TD) children and in individuals with the full WS genotype.

6.2 Methods

6.2.1 Participants

Data are presented from two individual cases with different genetic deletions occurring within or overlapping the WSCR. The two participants were recruited through collaboration with Annette Karmiloff-Smith at Birkbeck Centre for Brain and Cognitive Development, London. The extent of genetic deletion in each individual was determined using array comparative genome hybridisation (aCGH), by independent geneticists. HR is a female, aged 11;09 (years; months), and has a deletion of ~1 Mb which spans from the centromeric end of the WSCR at *NSUN5* to *GTF2IRD1* (72716513 to 73900000). The distal breakpoint lies within *GTF2IRD1* such that HR is partially deleted for *GTF2IRD1*, leading to reduced expression and thus haploinsufficiency for this general transcription factor (Tassabehji et al., 2005). The remaining three telomeric genes of the WSCR (*GTF2I, NCF1, GTF2IRD2*) are present in HR. JB is a male aged 14;02 and, in contrast with HR, has a deletion of ~2 Mb with a breakpoint in the distal WS region within (and so partially deleted for) *GTF2I* that extends beyond the WSCR in the telomeric direction (including a deletion of *NCF1* and *GTF2IRD2* within the WSCR) to *HIP1* (74133268 to 75333536). JB's deletion therefore contains 21 reviewed RefSeq genes based on the most recent build of the human genome (hg19). For the genetic deletions of HR and JB together with the 1.55-1.84 Mb regions typically deleted in patients with WS, see 6.2.1.1 Figure 21.



6.2.1.1 Figure 21. Schematic representation of genes located within the Williams syndrome critical region (WSCR) on chromosome 7q11.23, depicting common deletion sizes of ~1.55 - 1.84 megabases (Mb), and the individual deletions of HR and JB. Centromeric (cen), medial (mid) and telomeric (tel) low-copy-repeats (LCRs) A, B and C blocks (C cen not shown) are displayed in arrows flanking the single-copy gene region. The base pair positions (bp) of typical WSCR (~1.55 MB), HR and JB deletion points are based on build hg19 of the human genome. Gene codes in bold depict the 27-28 genes typically deleted in WS. Figure adapted and gene codes obtained from Schubert (2009). Figure not to scale.

Both participants completed a broad range of cognitive-functioning and visuospatial tasks. Testing took place in a quiet room at Birkbeck Centre for Brain and Cognitive Development, London. Visuospatial tasks included the object-based (OB) (monkey) mental rotation task, and visual perspective-taking (VPT) circle task presented in study 1, and the large-scale navigation strategies task presented in study 2. Performance by the two participants was compared to that of the typically developing (TD) individuals aged 5-10 years, and individuals with full WS earlier reported in studies 1 and 2.

6.2.2 Psychometric cognitive functioning measures

'Verbal', 'Non-verbal Reasoning', and 'Spatial' cognitive functioning were assessed using the British Ability Scales-II School Age (BAS-II) (Elliott, Smith, & McCulloch, 1996). 'Verbal' scores from the BAS-II are calculated from the Verbal Similarities and Word Definitions core scales, and Non-verbal reasoning is calculated from the Matrices and Qualitative Reasoning core scales. 'Spatial' scores are derived from the Recall of Designs and Pattern Construction core scales. The Raven's Coloured Progressive Matrices (RCPM) (Raven et al., 2003) was included as an additional measure of non-verbal ability as it has been established as a sensitive and reliable measure of non-verbal functioning in WS (Van Herwegen, Farran, & Annaz, 2011), and for consistency across studies.

6.2.3 Spatial measures

Two of the small-scale measures previously presented in study 1, and the large-scale virtual environment (VE) spatial task presented in study 2 were used in the present study in order to measure a diverse range of visuospatial abilities in HR and JB. As discussed previously, a behavioural distinction can be made between the mental transformation of objects and imagined self-rotations (perspective-taking) (Hegarty & Waller, 2004; Huttenlocher & Presson, 1973), with performance on these two types of task associated with activity in dissociable, although overlapping, neural systems (e.g.,

Zacks et al., 2000). Therefore, tasks requiring the use of different types of mental transformation (namely, object-based mental rotation and visual perspective-taking), as well as measures route-learning and egocentric and allocentric spatial-coding in large-scale space were conducted with these two participants.

6.2.3.1 Mental rotation (MR) task.

The ability to imagine the rotation of a 2D object at varying degrees of displacement from upright was measured using the monkey MR task. For full details of task design, see 2.2.3. In brief, participants were asked to view images of two monkeys above a horizontal line and one monkey below the line at varying degrees of rotation from upright, presented on a 14" laptop computer screen. Participants had to select which of the two monkeys on the top matched the rotated one underneath, indicating their response by pressing a left or right button on a keyboard in front of them. The MR task consisted of 28 rotation trials, and four control trials where the monkey underneath was not rotated (0° position). The test positions of the target monkey included 45°, 90°, 135° and 180° clockwise rotations and -45°, -90°, -135° anticlockwise rotations.

6.2.3.2 Visual perspective-taking (VPT) task.

The VPT task was used to examine participants' ability to imagine themself rotating around a circular array of four objects. For full details of task design, see 2.2.4. In brief, throughout the task, the participant was asked to imagine looking at the array from different viewpoints as well as a series of questions about the position of the different objects from the imagined perspectives (which object would be to your left, right, furthest, nearest). For consistency with the procedure used with TD and WS participants, both HR and JB were given a sticker on one hand (randomised left and right across participants) so that instead of declaring a left or right turn, they stated whether they would turn to their 'sticker' or 'no-sticker' side. Using two separate arrays, each participant was tested on a variety of imagined displacements of the self (45°, 90°, 135° and 180°, collapsed across clockwise and anti-clockwise rotations). The

test consisted of 28 rotation trials and four control trials where no imagined rotation was required.

6.2.3.3 Large-scale navigation strategies task.

The interactive VE maze presented in study 2 was used to examine the spontaneous strategy employed by each participant during large-scale navigation, and also whether the participant could develop an understanding of the spatial relationships between landmarks in the environment (an allocentric understanding of space), when required. For full task design, see 3.2.2. In brief, the VE presented participants with an environmental layout within which individuals could use either a sequential egocentric strategy (using the same sequence of left-right body turns) or an allocentric strategy to navigate, or a combination of the two (mixed strategy) to spontaneously navigate. As previously, spontaneous strategy trials and enforced allocentric trials were conducted with HR and JB. An 'allocentric score' was calculated from the enforced allocentric trials for both participants. As a further measure of their mental representation of the spatial relations of the environmental layout, at the end of the task participants were shown a selection of six birds-eye-view maps and asked to choose the correct layout of the environment through which they had been navigating.

6.2.4 Statistical analyses

Comparisons of performance on OB mental rotation, VPT and large-scale navigation by HR and JB with WS and TD data were conducted using Crawford-Howell modified *t*-tests for case-control comparisons (Crawford & Howell, 1998), developed to compare an individual's score to that of a small control group or normative sample (where $N < 50$). The program 'Singlims_ES.exe', was used to analyse the data (Crawford, Garthwaite, & Porter, 2010), available at: http://homepages.abdn.ac.uk/j.crawford/pages/dept/psychom.htm [last accessed 27/05/2014]. The modification of the independent samples *t*-test takes into account the mean and standard deviation for the comparison group on the task (and group *N*), and

the raw score of the single case. A point estimate of the effect size for the difference between the case and control (z-cc) with an accompanying 95% CI are also reported for statistically significant findings.

6.3 Results

6.3.1 Cognitive functioning

HR had a Verbal score of 80 (9th percentile) and Spatial score of 73 (4th percentile) on the BAS-II, demonstrating relatively impaired performance in both of these domains. In contrast, she presented with a relative strength in Non-Verbal Reasoning, with a score of 98 (45th percentile). HR's age-appropriate score of 32 on the RCPM also indicated a cognitive strength in non-verbal reasoning.

In contrast to HR, JB showed impaired performance on all measures of the BAS-II, with a Verbal score of 59 (0.3 percentile), a Spatial score of 47 (0.1 percentile), and a Non-Verbal Reasoning score of 65 (1st percentile). Similarly, JB presented with impaired performance on the RCPM, with a score of 18, an age-equivalent level of 7 years pointing to a score of only half his chronological age.

6.3.2 Spatial measures

Descriptive statistics for HR, JB, TD and WS groups from the Mental Rotation and Visual Perspective-Taking tasks are shown in 6.3.2.2.1 Table 14. Descriptive statistics for HR, JB, TD and WS groups for Navigational Strategies measures are shown in 6.3.2.3.1 Table 15.

6.3.2.1 Mental rotation (MR) task.

On the monkey mental rotation task, HR scored 18 out of 28 on rotation trials (64.29% correct). This was in line with the level of performance observed in TD 5 and 6 year-olds (t = -.19, p = *.42;* and t = -.28, p = *.39,* respectively), but reliably poorer than performance seen in TD 8 and 10 year-olds (t = -2.61, p= *.01*, z-cc = -2.68 [CI= -3.71 to -1.64], and t = -2.26, p = *.02*, z-cc = -2.33 [CI= -3.29 to -1.36], respectively).

HR's performance was at a similar level to that of individuals with full WS (t = .64, p = *.27*), who were at chance level. Conversely, JB scored 25 out of 28 on rotation condition trials (89.29% correct), demonstrating a high, near-ceiling level of performance on this task. Unlike HR, JB scored significantly above the WS group on this task, t = 2.03, p= *.03*, z-cc = 2.08 [CI= 1.29 to 2.87]. Although JB's performance was at a similar level to TD 8 and 10 year-olds, who perform at near-ceiling on this task, using the statistical methods noted above, scores were not reliably different from any TD groups (5 years: t = .81, p= *.22;* 6 years: t = .84, p= *.21*; 8 years: t = .19, p= *.42*; 10 years: t = -.04, p= *.48*).

6.3.2.2 Visual perspective-taking (VPT) task.

HR showed no deficits on this task, performing at ceiling with all 28 self-rotation responses correct, HR's score for left-right responses on the task being 100 percent (14/14). This reliably exceeds performance by individuals with WS (t = 4.44, p< .001, z-cc = 4.55, [CI = 3.04 to 6.04]), who show substantial deficits on self-rotations greater than 45˚ from their own vantage point. Similarly, JB showed no deficits on this task, apart from on trials when asked to state the 'nearest' object. This may have reflected a difficulty in understanding the meaning of the word, although he did get this correct on the control trial. On the trials requiring a left-right response, JB performed at ceiling with all 14 self-rotation responses correct. Again, this performance was greater than that observed in individuals with WS (t = 4.44, p< .001, z-cc = 4.55, [CI = 3.04 to 6.04]), and at a similar level to TD 8 and 10 year-olds (t = .69, p= *.25*; and t = .57, p = *.29*, respectively), many of whom also performed at ceiling. Of note however, is that neither HR nor JB performed reliably above TD 5 and 6 year-olds (p > *.05* for all), given that some individuals in these groups also performed well on this task. This may be a reflection of the stringent nature of the modified t-test, given that age-related differences were found between TD groups on this task (see 2.3.4.1).

In sum, HR and JB had similar performance on this task, demonstrating no deficit in VPT. Given ceiling performance, this task may not have been sensitive

enough to reveal differences between HR, JB and TD children. However, performances by both PD patients were indicative of a visuospatial profile different to that typically seen in individuals with WS. This high level of performance by JB was particularly surprising, given his poor scores on psychometric measures of cognition-functioning, although it is in line with his good mental rotation performance.

6.3.2.2.1 Table 14. Scores on mental rotation and visual perspective-taking tasks in HR and JB compared to Mean (SD) scores for TD and WS groups

	HR	JB	WS (N=20)	TD 5 years (N=16)	TD 6 years (N= 16)	TD 8 years (N=17)	TD 10 years (N=16)
Mental rotation *(% correct rotation trials)*	64.29	89.29	52.86 (17.48)	69.19 (24.11)	70.54 (21.61)	87.61 (8.29)	89.73 (10.90)
Perspective-taking *(% correct L/R rotation trials)*	100	100	32.13 (14.93)	46.88 (32.57)	60.92 (30.52)	91.27 (12.14)	91.96 (13.77)

6.3.2.3 Large-scale navigation strategies task.

HR learnt the route quickly, in only 4 trials. Although this was marginally slower than the ceiling performance seen in TD 10 year-olds ($t = 1.78$, $p = .05$, z-cc = 1.84 [CI = 1.01 to 2.64]), this was in line with TD children aged 8 years and younger and individuals with WS, who all reached criterion after a short number of trials ($p > .05$ for all). On trials examining the spontaneous navigation strategy, HR did not use a consistent strategy, but was incorrect on the first trial, then used an egocentric strategy for one trial and a mixed strategy on the final two trials. Comparable with spontaneous performance in typical adults (Iglói et al., 2009), TD children predominantly rely on the

use of a sequential egocentric strategy to navigate on this type of task (Broadbent, Farran, & Tolmie, 2014; Bullens, Nardini, et al., 2010), a strategy associated with preferential activation in the dorsal striatum and left hippocampus (Iglói et al., 2010). Individuals with WS, however, tend to rely on a mixed strategy on this task, likely due to the use of visual-matching and a reliance on landmarks for guidance. In contrast to individuals with WS, on trials examining the ability to use an allocentric strategy when prompted, HR was able to use this effectively, showing an allocentric strategy and ability to take the shortest route on 5/6 trials. The calculated allocentric score for HR on this task was at an age-appropriate level, in line with TD 10 year-olds (t = .95, p = *.18*), and at a level significantly higher than TD 5 year-olds (t = 1.76, p= .04, z-cc = 1.82 [CI = .99 to 2.62]); 6 year-olds (t = 2.96, p= *.01* z-cc = 3.06 [CI = 1.82 to 4.28]); and 8 year-olds (t = 1.89, p = *.04*, z-cc = 1.95 [CI = 1.12 to 2.76]). Similarly, HR scored significantly higher than individuals with WS (t = 4.79, p < *.001*, z-cc = 4.94 [CI = 3.17 to 6.69]), who demonstrate particular deficits in the use of spatial relational or allocentric frames of reference for navigation (see study 2). HR also chose the correct map layout, further suggesting an appropriate spatial relational representation of the environmental layout.

JB required a significantly greater number of trials than TD 8 and 10 year-olds to learn the route (t = 2.24, p = *.02* z-cc = 2.31 [CI = 1.38 to 3.22], and t = 4.64, p < *.001,* z-cc = 4.78 [CI = 3.01 to 6.53], respectively), reaching criterion only after 6 trials. JB's performance was not reliably different to that observed in TD 5 year-olds (t = .92, p = *.19*), 6 year-olds (t = .66, p = *.26*), or WS (t = .58, p = *.29*). On trials examining the spontaneous navigation strategy, JB made errors on two trials, but used an egocentric strategy on the other two trials, in line with the strategy predominantly observed in TD children. On trials examining the ability to use an allocentric strategy when required, JB made errors on half (3/6) of the trials. However, on the other trials, JB demonstrated an ability to use view-matching to search for the correct path, albeit in an inefficient and laborious manner that did not include taking the shortest route (2 trials as mixed strategy, 1 as allocentric). Although this resulted in an allocentric score

that could be considered delayed when contrasted with TD 10 year-olds, analyses did not yield any significant differences between JB and any TD group or the WS group, ($p > .05$ for all).

JB also correctly chose the environmental layout from the map selection. This suggests that JB may have developed a partial mental representation of the environmental layout. It should be noted, however, that a few WS participants also chose the correct layout despite showing no other use of an allocentric strategy for navigation. Although it cannot be concluded that JB developed an allocentric spatial representation of the environment to aid navigation, JB's large-scale spatial performance appeared stronger than typically observed in WS, and particularly unexpected given JB's very low scores on measures of non-verbal reasoning and psychometric measures of spatial intellect (BAS-II).

6.3.2.3.1 Table 15. Scores on navigation strategies VE task in HR and JB compared to Mean (SD) scores for TD and WS groups

	HR	JB	WS (N=17)	TD 5 years (N=16)	TD 6 years (N= 14)	TD 8 years (N=17)	TD 10 years (N=16)
Navigation strategies *(trials to learn)*	4	6	4.76 (2.08)	4.38 (1.71)	4.64 (1.99)	3.76 (.97)	2.75 (.68)
Navigation strategies *(allocentric score)*	10	4	2.94 (1.43)	3.00 (3.85)	3.00 (2.29)	4.65 (2.74)	6.31 (3.79)

6.4 Discussion

The uneven cognitive profile and identifiable genetic deletion in WS provides a unique model for examining the link between genes and cognitive-level outcomes. Elucidation of which of the 28 WSCR genes play a role in the visuospatial phenotype of WS, however, is challenging. The presentation of two genetically contrasting cases in

the current chapter provides insight both into the complex nature of mapping genetic contributions to human cognition, and the multifaceted nature of visuospatial cognition. Moreover, this study further highlights the possible combinatorial effects of genes within the WSCR, including the role of the general transcription factors and other telomeric genes on *some* aspects of visuospatial cognition.

Initial studies had implicated *LIMK1* as a major contributor to the visuospatial deficits in WS, on the basis of human partial deletion patients (Frangiskakis et al., 1996) and *limk1*-knockout mouse models (Y. Meng et al., 2002). *LIMK1* is expressed in various central nervous system tissues including cerebellum, spinal cord, and mesencephalon, as well as in the peripheral nervous system (Frangiskakis et al., 1996). Given the role of *LIMK1* in neurogenesis promoting axon outgrowth in the mammalian brain (Osborne, 2012), and possible involvement in synapse formation and regulation (Scott & Olson, 2007), it is a good candidate for a role in the WS cognitive phenotype. However, subsequent work on other partial deletion patients showed that if *LIMK1* does contribute, it is likely to be in combination with other genes at the telomeric end of the WSCR (Gray et al., 2006; Karmiloff-Smith, Grant, et al., 2003; Smith et al., 2009; Tassabehji, 2003; Tassabehji et al., 1999).

Drawing conclusions regarding human visuospatial cognition from studies (such as those aforementioned) that compare small-scale, table-top spatial deficits in WS with large-scale navigational deficits in the mouse is problematic given the very different cognitive demands placed on each species. Indeed, it remains unclear from such studies whether *LIMK1*, as well as other genes within the WSCR, contribute differently to cognitive or neural processes involved in egocentric compared to allocentric spatial coding. The current study examined both small- and large-scale visuospatial abilities in the same participants. This more in-depth analysis of visuospatial cognition is critical if we are to understand genotype/phenotype relations in WS.

An interesting pattern of strengths and weaknesses within the spatial-cognitive domain emerged in both participants. In particular, HR showed poor performance on psychometric measures of spatial cognition (as measured using BAS-II) and object-

based mental-rotation, alongside a relative strength in non-verbal reasoning (BAS-II and RCPM), and visual perspective-taking. Despite her deletion of over 24 genes in the WSCR, HR's performance was therefore not reflective of the cognitive profile of individuals with the full WS deletion. Indeed, HR performed at a level significantly above that observed in individuals with full WS on the VPT task, but below an age-appropriate level, and in line with individuals with WS on the MR task.

Neither was the pattern of performance across small- and large-scale tasks in HR necessarily typical. Relatively poor performance by HR both on the psychometric measures of spatial cognition and the mental rotation task, alongside proficient performance on VPT and large-scale navigation, reflects the multi-faceted nature of spatial cognition. In typical individuals, moderate correlations are found between performance on small-scale psychometric spatial measures and large-scale spatial abilities (Fenner et al., 2000; Hegarty & Waller, 2005) (for a further discussion, see chapter 4). However, in typical development, although performance on standardised tests of visuospatial memory correlate highly with route-learning ability, this is largely moderated by executive control (Purser et al., 2012). As such, although somewhat overlapping, small- and large-scale spatial abilities are partly dissociable and it can be inferred from the current findings that visuospatial abilities may be differentially affected by divergent genetic deletions.

What about the relationship between VPT and navigation strategies? Moderate correlations are also found in typical adults between VPT and the ability to use an allocentric navigation strategy in large-scale space (Kozhevnikov et al., 2006). Accordingly, HR's high level of performance on the VPT and navigation tasks (compared to individuals with the full WS deletion, who show substantial deficits on both of these tasks) suggests that she may be able to use this ability to spatially update the location of the self and to navigate successfully following a change in position in a large-scale familiar environment. That said, little is known about the extent to which performance on VPT tasks account for the variance in navigational abilities across development (see chapter 4). Indeed, the ceiling level of performance in JB on the VPT

task contrasted with poor navigational ability and low overall cognitive functioning (discussed below) suggests that they are not wholly associated, and may be differentially affected by genotypic variation.

In summary, in spite of HR's deletion of over 24 genes on the WSCR, including haploinsufficiency for *GTF2IRD1*, only some atypical visuospatial functioning was observed that resembles that of individuals with full WS. These findings suggest that the retention of the more telomeric 7q11.23 genes contribute to the relatively good large-scale visuospatial performance observed in HR, particularly in the face of her relatively low level of cognitive functioning as measured on 'Verbal' and 'Spatial' psychometric scales. This is in line with other research implicating a significant role for the GTF genes in the WS visuospatial profile (e.g., Antonell et al., 2010; Hirota et al., 2003). However, it remains inconclusive from this the extent to which each of the telomeric genes - *GTF2I, NCF1* and *GTF2IRD2*- play an equal role in large-scale spatial cognition.

The GFT genes *GTF2IRD1* and *GTF2I* share similar structure and function, coding for TFII-I proteins, which contain helix-loop-helix domains known as I-repeats (Roy, 2012). These TFII-I proteins are thought to act as transcriptional-activators and have a role in gene-regulation (Hinsley, Cunliffe, Tipney, Brass, & Tassabehji, 2004). Less is known regarding the function of *GTF2IRD2*, although it similarly codes for TFII-I-related proteins, and is thus thought to be another likely candidate for modulating the effects of others genes on the WSCR (Antonell et al., 2010; Tipney et al., 2004). *NCF1* however, is an NADPH-oxidase component involved in immune defence, and linked to the development of hypertension (Schubert, 2009). As such, it can be inferred that *NCF1* is less likely to be implicated in the WS visuospatial phenotype than those in the gene-modulating GTF family, although this cannot be established through the present findings.

If *LIMK1* (deleted in HR) plays a role in spatial cognition, then it may be that the preservation of the most telomeric genes within the WSCR allowed for the development of compensatory spatial strategies in HR. This is reflected in part by her

high level of performance, albeit with some atypical features, on the large-scale navigation task. That said, it is difficult to disentangle between whether such compensation is due to a genetic mechanism, or to the application of an alternative strategy that transpired through specific training. Further consideration of the modulatory role of both *LIMK1* and GTF genes on various visual processes within the WS phenotype, particularly in regards to their expression in different neural tissues (e.g., Castelo-Branco et al., 2007), is therefore imperative. As such, more comprehensive phenotypic studies at different levels of the nervous system would highlight more specifically the profile of visuospatial strengths and weaknesses in relation to the genetic underpinnings.

The profile of HR was presented alongside that of JB, an individual with a contrasting hemizygous deletion, which extends telomerically from within *GTF2I* to beyond the WSCR. Two quite differing cognitive profiles emerged from HR and JB. At the cognitive level, JB presented with profound impairments across the Verbal, Non-verbal and Spatial cognitive domains as measured using the BAS-II, and poor non-verbal reasoning measured by RCPM. Despite his preservation of the majority of the genes on the WSCR, this profile of deficits is expected, given the probable role of the telomeric genes on the expression of other genes (Osborne, 2012) as well as the role of *GTF2I* on general intellectual ability (C.A. Morris et al., 2003). It should be noted however, that JB's deletion comprises haploinsufficiency for up to 21 genes, many of which have unknown function. As such, it remains unclear what contribution they make to his profile. For example, haploinsufficiency for *HIP1* (deleted in JB) has been reported to be associated with neurological and neuropsychological deficits including epilepsy and autistic traits in other individuals with atypical deletions flanking the WSCR (Fusco et al., 2013). Indeed, a previous report of social cognition in JB revealed an autistic-like profile (Karmiloff-Smith et al., 2012). It is therefore important to take into account that JB has a large number of genes deleted outside of the WSCR, including haploinsufficiency for *HIP1* and is likely to have altered expression of *GTF2I*. Conclusions regarding comparisons of the two cases are therefore tentative. That said,

the inclusion of these two cases together provides insight into the differential effects of deleted genes within 7q11.23 on visuospatial abilities at different spatial scales, in the face of differing overall levels of intellectual ability.

Surprisingly, JB performed at a very high level on the small-scale monkey MR and VPT tasks, with scores significantly above those observed in individuals with full WS. By contrast, on the large-scale navigation task, and like individuals with WS, JB took a long time to learn the route, with performance below TD 8 and 10 year-olds. Allocentric spatial coding was also somewhat compromised, although not significantly different from any TD or WS groups (possibly due to the stringent nature of the modified t-test, given that differences were found across TD and WS groups on allocentric score, see 3.3.5.2). Despite these impairments in large-scale spatial coding, his performance reflected an overall profile unlike that typically observed in WS. Likewise, the uneven profile of JB's relative strengths and weaknesses across different spatial scales in the visuospatial domain was not comparable to that observed in TD individuals aged 5-10 years. Furthermore, given that JB performed at a high level on MR and VPT tasks, his relatively poorer performance on large-scale navigation cannot purely be considered a reflection of low general cognitive ability. Instead, these findings strongly indicate the role of other genes at 7q11.23 in mental rotation ability other than *GTF2I* or *GTF2IRD2* (for which JB is haploinsufficient). One possible candidate is the perseveration of *GTF2IRD1* in JB. Although others have reported that this gene alone is not sufficient to result in visuospatial deficits (e.g., Antonell et al., 2010), the current findings leave open the possible role for *GTF2IRD1* in mental rotation, albeit possibly only alongside haploinsufficiency of other genes on the WSCR. Similar robust conclusions cannot be made regarding the role of WSCR genes on VPT ability, given that both JB and HR performed at a high level on this task, and the vastly differing intellectual profiles of the two cases. However, there may be combinatorial effects of the GTFs and other more centromeric WSCR genes on VPT, although this can only be tentatively inferred given the difficulties in drawing direct comparisons from the two cases presented here.

Across the tasks in the current study, neither HR nor JB presented with a clear WS visuospatial cognitive profile, and both performed outside of the typically-observed variations in performance by individuals with full WS. A spatial advantage, particularly for mental rotation (Voyer, Voyer, & Bryden, 1995), is usually attributed to males, which could ostensibly be considered an explanation for the higher level of performance on this task by JB than HR. However, no gender differences were apparent in the TD or WS participants across the battery of spatial tasks employed here, including in mental rotation (see 2.3.9 and 3.3.5.2), suggesting that differences in the two cases presented here are not likely related to gender. Furthermore, on other tasks HR typically performed at a higher level than JB, which is more likely a reflection of their differences in overall intellectual functioning, than of gender.

These contrasting profiles pose an interesting question as to the combinatorial effects of genes at locus 7q11.23 on the WS visuospatial phenotype, particularly those at the telomeric end. As mentioned, HR's deletion includes that of *LIMK1*, a gene that had gained much attention in the search for mapping from genotype to spatial phenotype. Although *limk1* plays a critical role in long-term potentiation in the mouse hippocampus (Y. Meng et al., 2002), research in humans with atypical deletions in the WSCR has challenged the independent contribution of *LIMK1* to the visuospatial deficits seen in WS (e.g., Gray et al., 2006; Karmiloff-Smith, Grant, et al., 2003; Smith et al., 2009). More recently, the chromosomal region telomeric from RFC2, including *CYLN2*, *GTF2IRD1*, and *GTF2I*, has become a focus of interest as a possible contributor to the spatial cognitive profile in WS (Hoogenraad et al., 2002; Tassabehji et al., 1999). *CYLN2* (also known as *CLIP2*), for example, encodes *CLIP-115*, which is expressed in dendrites and cell bodies in a number of brain regions, including the hippocampus (Schubert, 2009), and *Clip2* knock-out mice present with brain and behaviour abnormalities associated with impaired cerebellar and hippocampal processes (Hoogenraad et al., 2002). HR is not deleted for *GTF2I* or other more telomeric genes, but her deletion does include a reduced expression of (and thus haploinsufficiency for) *GTF2IRD1*. Given HR's difficulties in mentally rotating objects, these results support

previous findings that haploinsufficiency for *GTF2IRD1* in combination with other 7q11.23 genes such as *CYLN2* or *LIMK1* may play a role in some of the (small-scale) visuospatial cognitive deficits observed in individuals with WS (Smith et al., 2009; Vandeweyer et al., 2012). This is supported by JB who is not deleted for either of these genes and performed well on the mental rotation task. Nonetheless, we cannot rule out that the deletion of the other more telomeric general transcription factors has impacted the expression of *CYLN2* and other 7q11.23 genes in JB (e.g., see Vandeweyer et al., 2012). It also remains unclear whether the deletion of other genes beyond the WSCR plays a role in the expression of intact genes within the WSCR.

Initially, the examination of visuospatial performance by HR and JB seems indicative of the additive effect of deleting each of the *GTF2I* family genes on the severity of cognitive impairment, and is in line with other findings in individuals with extended deletions, particularly those that encompass *GTF2IRD2*, who present with significantly greater neurological impairments than individuals with shorter deletions typical of WS (Porter et al., 2012). However, although we cannot dismiss the effects of other deleted genes in JB that extend beyond the WSCR on cognitive functioning, JB's high level of performance on small-scale mental rotation and VPT rules out the conclusion of a general deficit, and excludes the role of WSCR genes telomeric from *GTF2I* in these specific small-scale spatial abilities. Indeed, the preservation of most other genes within the WSCR in JB suggest that spatial skills may be differentially affected when GTF genes are deleted in combination with other more centromeric genes on the WSCR.

While the current study has highlighted candidate genotype/phenotype relations in the presentation of two contrasting case studies, it is clear that future studies need to adopt longitudinal and more in-depth analyses of genetics and cognitive phenotypes, measured across developmental time (Karmiloff-Smith, 2006). This is particularly important given that genes have changing patterns of expression throughout development, and environmental factors play a significant role in the modulation of gene expression across ontogeny (Osborne, 2012). This is reflected in the different

profiles of strengths and weaknesses expressed in WS in infancy compared to adulthood (e.g., Paterson, Brown, Gsodl, Johnson, & Karmiloff-Smith, 1999; Steele, Scerif, Cornish, & Karmiloff-Smith, 2013). The fact that genome function is modified over developmental time as a function of the epigenome requires assessments from infancy onwards of the details of the changing phenotype. Indeed, single gene dysfunction likely results in cascading effects at different cortical, subcortical and molecular levels of functioning that vary throughout development, highlighting the importance of applying a developmental and multisystem perspective to studying genotype/phenotype relationships in future (Scerif & Karmiloff-Smith, 2005).

With reference to genetics, it would be preferable to perform DNA and RNA sequencing to delineate the precise genomic boundaries of the deleted regions, and to examine gene expression patterns in the WSCR region and throughout the genome (Antonell et al., 2010). However, it is also critical that such detailed genetic studies be accompanied by in-depth phenotypic investigation, particularly at the cognitive level. The phenotypic analysis requires a broad spectrum of tasks, both standardised and hypothesis-driven, like in the current study, (see also, Gray et al., 2006) as examining performance only on standardised tasks (e.g., Antonell et al., 2010) does not yield a detailed account of phenotypic expression, particularly regarding the multi-faceted nature of spatial cognition.

A limitation of using case studies such as JB and HR is the difficulty in ascertaining whether gender influences gene expression in the WSCR, or whether the individuals have other genetic mutations elsewhere on their genome, outside the WSCR, that may affect general intellectual outcome. Furthermore, caution should be taken in making robust conclusions from such case studies, as direct mappings from individual genes to cognitive phenotype cannot be clearly defined, given the sometimes diverse contribution of genes to different aspects of cortical development (Karmiloff-Smith, 2006). In relation to the current study, numerous factors that include changes in gene expression across development, environmental influences, education and other individual differences may have contributed to the complex phenotypic outcomes in

both HR and JB. As such, genetic and phenotypic examination of other family members would be critical to complete the picture of such case studies, as well as being supplemented by appropriate animal models. In addition, such genotype-phenotype correlations should take into account the possible role of candidate genes in the development of other neural tissues. For example, Castelo-Branco and colleagues (2007) examined the contribution of the general transcription factors to the neural retinal phenotype in WS, finding patterns of visual impairment that were separate from the known cortical dorsal-stream phenotype. This highlights the important nature of in-depth phenotypic analyses in order to draw more robust conclusions as to the contributions of specific genes to cognitive phenotypes.

6.5 Conclusions

The examination of two individuals with such contrasting genetic deletions within the WSCR presented in this chapter provides further insight into candidate genotype relations to the WS visuospatial cognitive phenotype. The pattern of strengths and weaknesses within the visuospatial domain that emerged in both participants speaks, in particular, of the multifaceted nature of visuospatial cognition and the divergent effects of genetic deletions within the WSCR on different components of small- and large-scale spatial ability.

A deletion of over 24 genes on the WSCR in HR (including haploinsufficiency for *GTF2IRD1*) did not result in a phenotypic expression typically observed in WS, despite encompassing the majority of the genes typically compromised in individuals with the full WS deletion. Nor was HR's visuospatial cognition in line with what is observed in typical development. As such, the retention of the more telomeric genes in HR (including *GTF2I, NCF1, GTF2IRD2*) likely contributes to her relatively good large-scale spatial cognition, albeit with atypical features. In JB, an individual with a contrasting deletion in the distal WS region from within *GTF2I* presented with good performance on object-based mental rotation and VPT, alongside poor performance on large-scale spatial and general cognitive functioning measures. As such, these findings

indicate that even in the face of a stark intellectual deficit as seen in JB, mental rotation abilities in particular are not affected by genes extending telomerically from *GTF2I*. Indeed, although conclusions cannot be met from such case studies regarding precise genotype-phenotype mapping, the current study provides further insight into the complex, dynamic, and combinatorial role of different genes within the WSCR on disparate phenotypic expression within the visuospatial domain. Moreover these findings contribute to the ongoing debate regarding gene-brain-behaviour relations in WS, and highlight the importance of taking a multi-level approach to understanding the visuospatial cognitive phenotype associated with this disorder.

Chapter 7

General Discussion

7.1 Thesis overview

Examples of impaired visuospatial cognition in Williams syndrome (WS) have been frequently reported in the literature, and are often noted in comparison to relative strengths in other cognitive domains such as language and face processing (Bellugi et al., 2000). Evident in numerous small-scale tasks including visuospatial construction (Mervis et al., 1999), spatial orientation (Lakusta, Dessalegn, & Landau, 2010), and mental rotation (Stinton et al., 2008), poor visuospatial abilities are a hallmark and seemingly pervasive characteristic of the WS phenotype.

A reasonable conjecture therefore is that individuals with WS would also experience difficulties on tasks at different spatial scales, with the deficit pervading to large-scale navigational abilities such as learning a route or re-orientating oneself after getting lost. Indeed, this inference is made alongside parental reports of poor navigational performance in individuals with WS (J. Atkinson et al., 2001).

The studies presented throughout this thesis aimed to investigate the nature of large-scale spatial abilities in individuals with WS compared to typically developing (TD) children. An examination into the development of small-scale spatial abilities that rely on the use of different spatial frames of reference in study 1 (chapter 2), the use of different navigation strategies in typical development in studies 2 and 4 (chapters 3 and 5, respectively), and the relationships between small- and large-scale spatial abilities across development in study 3 (chapter 4), provided an important basis on which to understand atypical development. An analysis of the visuospatial profile of individuals with partial genetic deletions within the WS critical region (WSCR) in study 5 (chapter 6) also contributed to current discussions regarding the role of specific genes as well as their combinatorial effects on different components of visuospatial ability. This served to further highlight the multifaceted nature of spatial cognition, and inform an understanding as to the uneven cognitive profile in WS, even within the domain of visuospatial functioning.

This discussion chapter will provide an overview of the experimental outcomes presented throughout this thesis. Performance on tasks in TD children in studies 1-4 will be considered in light of the current understanding of developmental changes between 5 and 10 years of age in the ability to encode and use spatial information at different scales. The performance by groups of individuals with WS compared to TD children on these tasks will then be discussed to underline the specific levels and areas of impairment and atypical visuospatial processing in this disorder. This will be considered in respect to known cortical atypicalities in WS, although the speculative nature of defining brain-behaviour relationships in this manner are acknowledged. Furthermore, efforts to understand the nature of the large-scale visuospatial deficits in WS by examining genotype-phenotype relationships will be discussed in view of the findings from two individuals with partial WSCR deletions. Limitations of the experimental research conducted throughout this thesis will be addressed. The need for future research to take a multilevel and developmental approach to examine in-depth visuospatial phenotyping in WS will also be acknowledged. Finally, implications of the current findings for training and interventions for individuals with WS, as well as proposals for future research directions will be presented.

7.2 Performance in TD children on studies throughout this thesis

Together the findings from the studies presented in this thesis provide new insight into the development of large-scale spatial cognition, and particularly the way in which more complex cognitive processes that underlie spatial knowledge are acquired. For instance, the findings from studies 1 and 2 suggest that an adult-like pattern of performance in both small- and large- scale space is supported by the development of an ability to shift between egocentric and allocentric spatial frames of reference and translate spatial information from one frame of reference to another. This was seen to occur between 8 and 10 years of age. Firstly, an adult-like pattern of performance on the visual perspective-taking tasks that required the cooperative use of these two reference frames was not seen until this age in study 1. Secondly, only 8 and 10 year-

olds were able to flexibly switch to the use of an allocentric strategy to navigate when required to take short-cuts in study 2. These findings suggest that the ability to flexibly integrate different spatial frames of reference may underlie the development of more global representations of space and the ability to draw on and switch between different cognitive processes dependent on the task demands. These findings are in line with recent developmental studies that suggest there is a transition in the spatial frames of reference that children use for reorientation in both small- and large-scale environments, with an increase during the early school years both in the ability to use each spatial reference frame independently and the ability to use them cooperatively when required (Bullens, Iglói, et al., 2010; Moraleda, Broglio, Rodriguez, & Gomez, 2013; Nardini et al., 2006).

Of note here is that this suggests there may be a number of non-navigational contributors to navigational learning and the use of appropriate spatial frames of reference. As mentioned in 2.1.2 and 4.4, executive functions undergo a protracted course of development (Davidson et al., 2006; Diamond, 1990) and may underlie difficulties in flexibly shifting between spatial reference frames in younger children. The addition of tasks examining executive control, particularly inhibition and task switching, in the studies throughout this thesis would therefore have provided further insight into the extent to which these abilities are related to online navigational performance. Indeed, studies previously examining the relationship between small and large-scale visuospatial abilities have found that significant correlations are mediated by executive control (Purser et al., 2012).

Traditional behavioural frameworks of the development of large-scale spatial knowledge (e.g., Siegel & White, 1975) propose both an ontogenetic and a microgenetic shift from landmark knowledge to route knowledge, and finally to survey knowledge; with qualitative differences between each stage. Although this classification system has been somewhat debated, it has provided an important basis on which to understand spatial navigation and only few recent attempts have been made to propose alternatives (e.g. see, Chrastil, 2013; D. R. Montello, 1998). Even then, these alternative frameworks only hypothesise the advancement of spatial knowledge in typical adults,

without consideration for changes across development. The studies in this thesis therefore contribute to our understanding of the nature of the development of large-scale spatial abilities, suggesting that there are a number of cognitive processes underlying the use of each stage of navigational knowledge, and that these may be subserved by the use of different spatial frames of reference and have distinct neural correlates.

Prior to the studies in this thesis, there was limited acknowledgement in the literature as to the way in which the use of different spatial frames of reference (i.e., egocentric and allocentric) relate to the different aspects of large-scale spatial knowledge as laid out by hierarchical theories of cognitive development. That said, it has generally been considered that landmark and route knowledge are associated with the use of an egocentric reference frame, and survey knowledge with an allocentric frame of reference (Wen, Ishikawa, & Sato, 2013). Integrating these levels of understanding (spatial frames of reference and stages of large-scale spatial knowledge) has provided insight into the flexible and dynamic nature of visuospatial cognition, and also the possible constraints on using different aspects of spatial knowledge across development.

Study 1 examined the ability to mentally manipulate a representation of either an object or the self to a different imagined location or viewpoint, respectively. TD children demonstrated an increase in both of these abilities (object-based (OB) mental rotation and visual perspective-taking (VPT)) between 6 and 8 years. This was in line with previous findings in TD children of similar age (Huttenlocher & Presson, 1973; Newcombe & Huttenlocher, 1992). Moreover, TD 5 and 6 year-olds presented with a different pattern of performance to TD 8 and 10 year-olds, with the older groups showing a pattern more in line with typical adults[1]. As mentioned above, this was particularly so for performance on the VPT tasks. For instance, a linear decline in accuracy with greater degree of required imagined displacement of the self (particularly between 90° and 180°) is not seen in typical adults (Zacks et al., 2000). This has been attributed to the use of an alternative strategy by adulthood, such as employing 'blink transformations' to immediately mentally transpose the self to an alternative perspective

[1] Based on previous research in typical adults on comparable tasks (Zacks, 2008)

(Kessler & Thomson, 2010; Wraga et al., 2000; Zacks & Michelon, 2005). This was a similar pattern to that observed in the TD 10 year-olds in the present study, suggesting an adult pattern of performance emerges by this age.

Object-based mental rotation requires the use of an allocentric frame of reference, by which an understanding of the relationships between items in an array or between parts of an object is required (Kozhevnikov & Hegarty, 2001). On the other hand, VPT tasks are thought to rely on the use of an egocentric reference frame to determine the location of an object relative to the intrinsic axis of the observer (Wraga et al., 2000; Wraga et al., 2005). Not only do typical adults present with a different pattern of performance on VPT tasks compared to OB rotation, behavioural studies have found an advantage for self-rotations (VPT) both in terms of accuracy and reaction times (e.g., Amorim & Stucchi, 1997; Creem et al., 2001; Wraga et al., 2000). Neuroimaging studies have shown that activation of the parietal-occipital sulcus, including the retrosplenial cortex, positively correlates with self-rotation performance (Lambrey et al., 2012). This region is also associated with the spatial updating of egocentric locations within an allocentric frame of reference (e.g., Burgess, Becker, King, & O'Keefe, 2001). Lambrey and colleagues (2012) therefore suggest that the ability to translate between an egocentric and allocentric reference frame (and therefore perform automatic 'spatial updating' of a viewpoint as a consequence) underlies the advantage for VPT compared to OB rotations in some adults. Despite the use of different spatial frames of reference for the mental rotation of objects (OB) compared to imagined self-rotations (VPT), a similar age of development for these two abilities was observed in study 1, with improved performance between 6 and 8 years. However, the later development of an ability to switch successfully between the use of an egocentric and allocentric frame of reference (Nardini et al., 2006; Nardini et al., 2009) may underlie the advantage for VPT in older children and adults, but not for younger children. This was supported in this study, with an adult-like pattern of performance on the VPT task not evident until 8-10 years of age.

The findings from study 2 are further indicative of this later development of an ability to switch between spatial frames of reference when required for large-scale

navigation. In this study, when spontaneously navigating through a familiar virtual environment, TD children predominantly followed the same previously-learnt pattern of body turns to reach the goal; namely, a sequential egocentric strategy. When required to rely on the use of an allocentric spatial reference frame in order to find a short-cut however, a change was seen from youngest to oldest TD children. Only TD 8 and 10 year-olds demonstrated a significant difference in allocentric ability between spontaneous and enforced allocentric trials. This is in line with previous research in children of comparable chronological age in large-scale environments (Bullens, Iglói, et al., 2010).

Successful performance on the complex navigational task of finding short-cuts therefore requires the ability to understand the location of landmarks in relation to other landmarks, as well as being able to continuously mentally update the location of the self within the broader context of the environment. These findings also correspond to more recent cognitive frameworks that propose the nature of large-scale spatial knowledge in typical adults is flexible and multidimensional (Chrastil, 2013). Chrastil (2013) proposes that the ability to transform between ego- and allocentric perspectives relates to a cognitive sub-process associated with both graph knowledge (an understanding of how locations are connected to each other, but without necessarily containing metric information) and survey knowledge, and is supported by hippocampal, parahippocampal and retrosplenial cortices. In sum, both studies 1 and 2 of this thesis have shown that the ability to understand the location of a goal in relation to the self and other environmental locations, and to continually update this when walking through the environment, requires the successful translation between an allocentric and egocentric frame of reference, and begins to emerge from 8 years of age.

In adults, small-scale VPT ability and performance on large-scale navigation tasks that require updating self-to-object representations following movement are moderately correlated (Kozhevnikov et al., 2006; Palermo et al., 2008). This is indicative of shared underlying processes associated with performance on tasks at these different spatial scales. Relationships between OB rotation ability and navigational performance, on the other hand, are more negligible (Hegarty et al., 2006; Hegarty &

Waller, 2005). Moreover, previous developmental studies have found only marginal correlations between small- and large-scale spatial tasks in children, if any (Quaiser-Pohl et al., 2004). Any significant correlations in TD populations are found to be mediated by other cognitive factors such as inhibition (Purser et al., 2012). The positive relationships in TD 10 year-olds between VPT ability and large-scale allocentric knowledge in this thesis (study 3) provides support for a developmental increase in the use of common underlying cognitive processes to perform these tasks by this age. Such associations were not evident in TD children younger than 10 years of age. Given that TD 8 year-olds in studies 1 and 2 also demonstrated an ability to switch between reference frames however, it would be expected that correlations between these tasks would also be seen in this group. It may be that the results reflect an issue of limited statistical power (as indicated in results of power analyses reported in Chapter 2), warranting the use of larger TD sample sizes to verify these findings. The small group sizes in these studies are particularly emblematic of studying individuals with rare genetic disorders (an issue that is similarly reflected in the need to select a large age range of individuals within the WS population, given the limited sample). This may have been a greater issue in other analyses that require greater sample sizes. For instance, one-way ANOVAs and repeated measures ANOVAs for 5 groups, used throughout the studies in this thesis require sample sizes of 15 – 40 participants per group (based on *a priori* power analyses; α 0.05, effect size 0.50, 1-β at 0.8). The smaller sample sizes reported here may therefore have resulted in type-2 errors. To account for this, stringent Bonferonni corrections for multiple comparisons were not included, even for multiple correlational analyses. Of course, this however may have inadvertently resulted in significant findings being the result of type-1 errors, and so without more adequate sample sizes and correctional analyses, the results should be considered tentatively.

As an alternative to the non-significant findings in the youngest TD children being due to limited statistical power, the results may indicate that below 10 years of age, performance on tasks at different scales are supported by different cognitive

processes, even though the flexible use of different spatial reference frames for small- and large-scale tasks independently is seen by 8 years of age.

As well as the changes in TD children in the ability to flexibly use spatial frames of reference, the type of spatial information used by TD children was also examined in this thesis. Results from study 4 showed that during route-learning, TD children aged 5-9 years do not only obtain spatial information about the location of landmarks, but are able to simultaneously acquire sequential body-based information. This is not fully accounted for in hierarchical models of spatial knowledge, which propose a stage-like process in the types of information gleaned from an environment following experience. This is more in line with recent frameworks of large-scale spatial navigation (e.g., Chrastil, 2013), that indicate sequence learning and response learning are dissociable aspects of the broader category of route knowledge. In this study, sequential route information of a large-scale environment (sequence learning) was encoded implicitly in TD children, alongside the more explicit learning of an egocentric response-strategy (response learning) that related to learning associations between a particular environmental location and a required action. It should be noted however that sequence learning may be further split into two sub-processes; the ability to remember an ordinal sequence of landmarks compared to the ability to recall a sequence of body turns in an environment without landmarks. This is discussed later (see 7.3) in relation to different cortical regions that may be associated with these processes.

In sum, the development of the ability to flexibly shift between the use of different spatial information and reference frames may underlie the observable developmental changes in strategy use and proficiency on spatial tasks. The results from TD children in this thesis suggest that performance on mental transformation tasks (both OB and VPT) improve significantly between 6 and 8 years of age. However, an adult-like *pattern* of performance on VPT tasks does not occur until between 8 and 10 years, in line with the development of an ability to flexibly switch between an egocentric and allocentric reference frame (although the addition of tasks examining difference elements of executive functioning, such as task switching and inhibition, would have been beneficial in substantiating these claims). This was further supported

by the later use of an allocentric reference frame to update the location of the self, following movement in a large-scale environment only by 8 and 10 year-olds. Stage theories may be somewhat useful for understanding behaviour and the main categories of mental representations that can be formed in large-scale space. However (as seen in study 4), there are likely to be different underlying cognitive processes and sub-processes involved within each main category of spatial knowledge, which are not accounted for by traditional frameworks.

7.3 Visuospatial abilities and navigation strategies in WS

The exploration into the development of large-scale spatial cognition and navigation strategies in TD children throughout this thesis provided an important basis on which to examine atypical development of large-scale spatial abilities in WS. In the studies presented here, groups of individuals with WS performed at the level expected based on non-verbal ability (in line with TD 5-6 year olds) on a number of tasks. However, on some aspects of the tasks and under certain conditions, individuals with WS scored below this level and demonstrated an atypical pattern of performance. The results are informative not only to the syndrome-specific areas of relative strengths and weaknesses within the visuospatial domain, but also speak of the multifaceted nature of visuospatial cognition.

In study 1, the WS group were at chance level for all imagined rotations on the OB monkey task (requiring the mental transformation of an image), and at chance on imagined rotations of the self (greater than 90°) around an array (VPT circle task). However, the WS group scored above chance on imagined rotations of the self to 90° on the VPT path task. Given the specific spatial frames of reference required for performance on these tasks (as mentioned above), these findings are indicative of profound impairments in WS in the use of both egocentric and allocentric reference frames to perform mental transformations. This is in line with other small-scale studies that report; impairments in both these spatial reference frames (Bernardino et al., 2013); impaired mental rotation (Farran & Jarrold, 2004; Stinton et al., 2008); and poor VPT

(Farran et al., 2010) in this group. A recent developmental trajectory study into OB mental rotation and VPT in WS found an improvement in OB rotation in WS with development (between 6 and 33 years of age; verbal mental age range 3;3 – 11;1 years; months), but no changes in VPT ability (Hirai et al., 2013). The authors concluded that OB rotation ability develops slowly in WS, whereas processes involved in VPT such as theory of mind are particularly impaired leading to more a severe detriment to this ability. This pattern was partly reflected in study 1 in this thesis in the positive relationship between age and score on the OB monkey rotation task in the WS group, with no correlations found between VPT scores and age in the WS group. Similarly, WS verbal ability (BPVS) correlated with monkey rotation score, although this was driven by chronological age. Of note however, no correlations between age and OB circle task in WS were found in study 1, which may be indicative of the different levels of difficulty in the two OB tasks used (OB monkey and OB circle task).

In contrast to the findings in study 1 on the OB monkey task, Hirai and colleagues found above-chance performance in the WS group on OB mental rotation, suggesting that the images used in the present study may have been more challenging to rotate. For this reason, it may be difficult to make robust conclusions regarding the extent of difficulties mentally rotating images in WS from this study, as the OB rotation scores may be below that of the true ability level in WS. This may also have implications for the TD data on these tasks, suggesting that with a less complex rotation image, TD children may perform at a higher level, and reach above-chance levels at a younger age than observed here. Furthermore, both the WS group and TD 5 year-olds in the present study performed at floor level and so any true differences between the groups on mental rotation ability may have been masked.

Even though performance in the WS group on rotation tasks was in line with TD 5 year-olds, the results of study 1 demonstrate an atypical pattern of performance in the WS group compared to TD children. A propensity to approach rotation problems using one's own stationary viewpoint and failure to transpose this reference frame resulted in a disproportionate number of egocentric errors in the WS group. This was the first indication in this thesis that individuals with WS may approach spatial tasks in a

different way to TD individuals, and do not just display a delay in the development of their abilities. In essence, individuals with WS may be failing or succeeding on tasks for different reasons than TD individuals.

The navigational strategies used in large-scale environments in WS were examined in studies 2 and 4, and the extent to which performance on large-scale tasks can be accounted for by small-scale task performance was examined in study 3. Results from studies 2 and 4 demonstrated that individuals with WS have difficulties not only in the use of an allocentric reference frame, but also in the use of a sequential egocentric strategy to navigate. Impairments in WS in the use of an allocentric strategy in large-scale space had been previously demonstrated in real-world environments (Farran et al., 2010). The VE studies in this thesis extend these findings to demonstrate that allocentric knowledge in WS does not develop even following extensive experience in an environment or when participants are directed to take into consideration the layout of an environment in order to take short-cuts (study 2). Instead, individuals with WS were found to rely on the use of an inflexible and relatively inefficient visual-matching strategy to navigate, associating individual landmarks with a specific body-based response. This was a finding further substantiated in study 4. On the tasks in study 4, TD children were able to resort to the use of their memory of the sequence of body turns through a maze when required (i.e., when no landmarks were present or when landmarks were removed), which may have been learned implicitly alongside more explicit association-response learning between landmarks and direction decisions. In contrast, the WS group relied more heavily on the presence of landmarks than TD children, resulting in significantly greater detriment to performance following the removal of these visual cues.

Navigation in a real-world environment allows for internally-generated idiothetic cues such as proprioception, vestibular feedback, and optic flow to be used to support learning and processing of different spatial frames of reference (particularly an egocentric frame) (Boccia, Nemmi, & Guariglia, 2014). Given the lack of actual movement in desktop virtual environments such as those used here, it may be that this was a limiting factor in the successful development of spatial sequential learning in WS.

However, given that TD children were able to develop an understanding of the sequence of body turns throughout a route, and successfully switch to using this strategy when other environmental cues were no longer available, it is unlikely that the lack of idiothetic cues was a substantial contributing factor to the difficulties in WS. For further limitations in using VEs to assess spatial knowledge in WS, see 7.5.3.

An association-response strategy relies on the use of an egocentric frame of reference, as the navigator encodes an association between their viewpoint and a given action. The parietal cortex plays a role in the representation of space using an egocentric frame of reference (Galati et al., 2000; Shelton & Gabrieli, 2002, 2004). This brain region has been shown consistently to be atypical in structure and function in WS (Eckert et al., 2005; Kippenhan et al., 2005; Meyer-Lindenberg et al., 2004). The results in study 4 are indicative of a relative strength in egocentric response-learning in this group, suggesting that not all parietal lobe functions are equally compromised in this disorder. The use of a sequential egocentric strategy is, however, impaired in WS. On examination of the different types of egocentric strategies used in large-scale space, neuroimaging studies have shown that although egocentric *response* strategies are associated with preferential activation in the caudate and parietal cortex (Hartley et al., 2003; Marchette et al., 2011), the learning of egocentric spatial and temporal *sequences* in an environment depends on the integrity of the hippocampus (Foster & Knierim, 2012; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Iglói et al., 2010; Kumaran & Maguire, 2005; Maguire et al., 1997). The dorsolateral prefrontal cortex (DLPFC), calcarine sulcus and lingual gyrus also play a role in the successful encoding of sequences in large-scale space (Nemmi, Boccia, Piccardi, Galati, & Guariglia, 2013). This suggests that there may be a network of brain areas involved in the encoding and storage of sequential information. For instance, the encoding of the order of landmarks throughout a route may elicit activity in different cortical areas to those involved in the implicit encoding of the sequence of body turns required to navigate through a given route. Given these may be separate processes, it is therefore not reasonable to assume that each egocentric strategy would be equally impaired in WS.

Atypical structure and functioning in the hippocampal formation in WS (Meyer-Lindenberg et al., 2005) may be associated with difficulties in using a sequential egocentric strategy as seen in these studies. Throughout the thesis, difficulties with allocentric processing both on small- and large-scale tasks in WS have been similarly attributed to atypical development of the hippocampal region. This is based on findings from typical adults that implicate the role of the hippocampus in allocentric processing on small-scale rotation tasks (Lambrey et al., 2012), and the development of environmental relational knowledge (Burgess, 2008; King et al., 2002). However, the brain imaging studies in WS cited above have similarly focused on cortical abnormalities in adolescents and adults. It may be important therefore to take into account a developmental view of atypical brain development in WS before more robust inferences regarding causality can be made. This will be discussed in more detail in 7.5.

A response strategy such as visual-matching used in the WS group (as evidenced and discussed in study 4) could alternatively be considered a non-spatial strategy, which does not require knowledge of the order of landmarks or any distance and directional information that connects different aspects of the environment. Instead this could entail independent learning of the response to each environmental landmark using verbal coding, and without consideration for the location of the landmark in relation to other parts of the route. Relative strengths in verbal abilities in WS may therefore support the use of such strategies. Indeed, Farran, Courbois, Van Herwegen, and Blades (2012) found that verbal labelling in WS improved knowledge of the sequence of turns, an aspect of route knowledge. That said, it cannot be concluded from study 4 which elements of the visual scenes individuals with WS were using, and whether they were able to encode configurational knowledge within the scene to support recognition and decision-making. Therefore, further research is needed to examine the nature of using visual matching in WS, to elucidate the processes involved.

The reliance on a visual-matching strategy would have important connotations for individuals with WS when traversing through an environment that contains a number of similar-looking or identical landmarks. If additional spatial information including the order in which a given landmark came in a sequence is not successfully

coded, then an incorrect response may be executed. For instance, if a route contains two post-boxes, one at which a right turn is required and the other a left turn or to continue straight, without accurate information regarding the sequence in which these two post-boxes had been experienced, an incorrect decision could be made. Further research is required to examine this, and whether individuals with WS would be able to use verbal coding to support any conflicts in the required body-based response.

In relation to cognitive frameworks of large-scale spatial cognition (e.g., Siegel & White, 1975), results from previous navigation studies suggest that individuals with WS have difficulties in developing survey knowledge (Farran et al., 2010), but are able to successfully learn a route and use environmental landmarks (Farran, Courbois, Van Herwegen, & Blades, 2012), albeit only to a level expected based on non-verbal ability. This is in line with successful use of an egocentric (viewpoint-dependent) reference frame but not allocentric (viewpoint-independent) on small-scale tasks in WS (Nardini et al., 2008). The results presented in this thesis however suggest that navigational abilities cannot be categorized simply into landmark, route and survey knowledge as three separate components. Here, individuals with WS were found to be impaired in the use of both allocentric and egocentric spatial frames of reference, although some cognitive processes relating to route knowledge that use an egocentric reference frame may be more impaired than others. Indeed, there may be a variety of cognitive processes that require egocentric knowledge. This may be related to the different brain regions that support the use of these different egocentric sub-processes, as highlighted above. In brief, the ability to learn a route through an environment on the basis of a simple response strategy requires the use of a viewpoint-dependent egocentric reference frame and knowledge of the specific action required at that location. Individuals with WS were relatively unimpaired on this compared with sequential egocentric learning, which entails knowledge of the ordinal relationships between the navigator and parts of the route.

According to a recent taxonomy by Chrasil (2013), the difference between route and graph knowledge (graph knowledge being situated between route and survey knowledge, see 1.2.2.1 Table 1) is that graph knowledge entails an additional ability to

understand the location of landmarks relative to other places within the larger environment, and also the ability to flexibly shift between an egocentric and allocentric perspective. This is in turn different to survey knowledge, which requires additional metric information about distance and angles, allowing for more complex and complete large-scale spatial knowledge. If large-scale spatial cognition in WS was limited to difficulties in flexibly switching between both perspectives (as observed in TD children above), this could relate to executive functioning impairments in WS (Carney, Brown, & Henry, 2013; Costanzo et al., 2013), although Menghini et al. (2010) found that shifting ability in WS is relatively unimpaired compared to other executive functions. However, deficits in the independent use of both of these spatial frames of reference suggests that switching difficulties would not fully account for the extent of the visuospatial impairments experienced by individuals with WS. That is to say, impairments in both egocentric and allocentric strategies alone would lead to deficits on complex navigation tasks, regardless of whether a task requires the flexible integration of the two perspectives. That said, the inclusion of tasks examining cognitive flexibility may have provided insight into the extent to which this ability plays a role in navigation, and particularly how this compares to the pattern seen in TD children.

Results of correlational analyses reported in study 3 found no significant relationships between performance on small- and large-scale spatial abilities in WS. This suggests that, although the findings in studies 1, 2, and 4 show that individuals with WS may be impaired in the use of both spatial frames of reference, the underlying cognitive processes involved at different scales are not necessarily related. Floor level performance on some tasks and wide-ranging variability on other tasks in the WS group may have contributed to these non-significant findings. However, given the lack of correlations in TD children below 10 years of age on most tasks, this implies that performance on spatial tasks at different scales in WS and young TD children are dissociable, and should be treated as such. This has important implications for making inferences about environmental abilities in WS and TD children based on table-top measures of visuospatial ability. Together these findings suggest that visuospatial cognition is multifaceted. This was further supported in study 5 in an examination of

the genetic contributions to the WS visuospatial phenotype. This study concluded that there may be multiple underlying influences on outcomes of distinct visuospatial abilities and at different spatial scales. This is discussed further in the following section.

7.4 Genotype-phenotype correlations in WS

Given that WS arises from an identifiable genetic deletion, it is appealing to search for direct gene-behaviour mappings in order to elucidate which of the WS genes play a role in the visuospatial impairments associated with the disorder. An in-depth phenotyping of visuospatial abilities in two patients with partial genetic deletions on the WS critical region (WSCR) of chromosome 7 (study 5) provided some insight into the candidate genes associated with visuospatial impairments in WS. The results pointed towards a role of the telomeric general transcription factor (GTF) genes, and their possible combinatorial effects on different aspects of visuospatial cognition. This was in line with other work that has found more severe cognitive impairments are associated with the deletion of the genes telomeric to *ELN*, that include the three GTF genes (Frangiskakis et al., 1996; Heller et al., 2003). This is unsurprising given that the three GTF genes in the WSCR in particular (*GTF2I, GTF2IRD1* and *GTF2IRD2*) code for proteins that activate or repress the expression of other genes (Young et al., 2008).

In the study presented in this thesis, one participant (HR) was haploinsufficient for 24 out of the 27 genes in the WSCR, although she presented with a profile in line with TD children on a number of tasks. Of note is that HR was haploinsufficient for one of the GTF genes (*GTF2IRD1*), and yet this alone was not sufficient to result in a WS visuospatial profile. Even from the in-depth phenotypic investigation in this thesis, the role of individual WSCR genes on specific spatial abilities remains elusive. Indeed, conclusions regarding whether each GTF gene plays an equivalent role in coding for visuospatial functioning could not be met. One finding from the other participant (JB) however, indicates that genes telomeric to *GTF2I* are *not* implicated in mental rotation ability. This was demonstrated as JB was deleted for these genes and yet demonstrated relatively strong mental rotation ability, even in the face of severe general cognitive

impairment. Further tests of mental rotation in this individual would be favourable to help confirm these findings.

The discussion of study 5 accords with conclusions of previous chapters as to the multifaceted, and divisible nature of visuospatial cognition. Although it is clear that the visuospatial cognitive profile in WS (as well as other phenotypic traits) arises from the haploinsufficiency of genes within the WSCR, it is likely that different genes play a role in the expression of distinct aspects of visuospatial cognition. These may in turn be modulated to different levels by the GTF-family genes. Although visuospatial abilities may be somewhat overlapping, changes from childhood to adulthood in the extent to which visuospatial tasks are correlated (both between and within different scales) are indicative of the dynamic nature of gene expression and cognitive functioning over developmental time. Furthermore, some spatial abilities may have a stronger genetic component than others, suggesting that a concurrent examination of genetic, brain, environmental and developmental factors is crucial. This is the case not only for understanding the nature of deficits in WS, but also for understanding changes in visuospatial cognition throughout typical and atypical development.

7.5 Approaches to examining the WS visuospatial profile

7.5.1 Using a multilevel approach

The studies presented in this thesis have, for the most part, examined large-scale visuospatial cognition in WS at the behavioural level. Although the relationships between genotype and visuospatial phenotype in WS were addressed, further analysis of the nature of visuospatial impairments in this disorder at different levels (brain, genes, cognition and behaviour) would be an important extension of this work.

An examination of the neural correlates of large-scale spatial cognition in WS was beyond the scope of this thesis. Instead, known abnormalities in brain structure and functioning in WS were presented as possible indicators to the specific spatial difficulties that would be encountered in this disorder. It is important to note therefore

that in the same way that attempting to make direct genotype-cognitive phenotype mappings is problematic (see also, Karmiloff-Smith, Scerif, & Thomas, 2002); drawing conclusions regarding one-to-one mappings of brain to behaviour may be questionable.

Imaging studies have revealed a reduction in overall brain volume in WS by ten to fifteen percent, with some areas such as the parietal-occipital lobes disproportionately decreased (Chiang et al., 2007). In fact, findings have consistently pointed to reduced grey-matter density in posterior parietal and occipital areas in WS (Eckert et al., 2005; Meyer-Lindenberg et al., 2004; Reiss et al., 2004). Reduced volume in these visual-spatial processing areas are often taken to infer an altered level of cortical integrity. However decreases in brain volume may not necessarily equate to a reduced level of functioning. In line with this, Menghini et al. (2011) argue that interpretations of brain imaging studies in WS when images have been transformed by normalisation strategies to fit standardised templates, should be made with care. Some studies however, have examined relationships between structural and functional changes in the brains of individuals with WS. For example, work by Meyer-Lindenberg et al. (2004) found that hypoactivation in the parietal dorsal stream and reduced grey matter in parietooccipital and intraparietal sulcus contributed to functional abnormalities on spatial construction tasks. Another study by this group found reduced metabolism and activation of the anterior hippocampal formation in response to visual stimuli in WS, a finding that was in line with an altered structure of this region (Meyer-Lindenberg et al., 2005).

Findings from the studies presented in this thesis suggest that reduced functioning in the use of both egocentric and allocentric frames of reference in adults with WS may be related to the structural and functional changes in the cortical areas associated with these tasks in typical individuals. However, despite these findings being in line with neuroimaging studies in adults with WS, the same may not hold true across development. The notion that there are individual cortical regions compromised in WS while other brain areas remain intact may be simplistic and does not take into account the dynamically changing nature of the brain or the different influences of genes and environment over developmental time (Karmiloff-Smith, 2012). For instance, there are likely to be a number of downstream effects of atypical brain maturation on

connectivity and the integrity of different cortical areas (Karmiloff-Smith, 2006). For this reason, it does not suffice to say that impaired visuospatial abilities and atypical navigation strategies in children with WS are entirely a result of compromised parietal and hippocampal regions, as it may be that atypical development of spatial cognition itself drives abnormal functioning in these brain regions. Indeed, there may be some brain regions more vulnerable to disruption from atypical development than others. Therefore, inferences about cognition across the lifespan based on adult WS brain morphology and vice-versa, should be taken cautiously.

Although research examining atypical cortical structure and function in WS can inform our understanding to some extent of the types of visuospatial deficits in adults with WS, little is known about the actual neural correlates of spatial processing in WS, particularly during navigation tasks. Future studies would therefore benefit from the use of functional neuroimaging techniques to examine whether the same cortical regions are preferentially activated in WS as TD individuals during tasks where there are impairments, but also where behaviour is at a comparable level, or where similar strategies are used. Indeed, that which presents as being intact at the level of behaviour may not involve the same neural substrates as seen in typical individuals (Karmiloff-Smith et al., 1997).

Given this, and the previous discussion into examining genetic contributions to spatial deficits in WS, it is important to take into account a multi-level perspective of visuospatial impairments in WS. In addition, the role of the environment, including the role of education and parental support in learning to navigate and the extent to which this would have an impact on the strategies and performance in WS are important factors to consider. Furthermore, it is essential not just to look at different levels of description, but also the way in which these interact throughout development. An examination of visuospatial impairments in WS within a developmental framework is best placed to delineate the causes of change with maturation and over time.

7.5.2 Using group comparisons

Throughout this thesis, groups of individuals with WS were compared to TD children between 5 and 10 years of age. This age range of the TD groups incorporates the ages at which there is a significant progression in performance on these tasks to adult levels. In each experimental study, the WS group was in line with the oldest TD children (TD 9-10 years) on measures of verbal ability and in line with the youngest TD group (TD 5 or 6 years) on measures of non-verbal reasoning, representing the strongest and poorest cognitive abilities in WS, respectively. Therefore, any differences between the WS and TD groups on any experimental measures could not be accounted for by level of general intellectual impairment. Previous research has shown consistently that adults with WS usually perform at the level of TD 4 to 6 year-olds on visuospatial tasks (Farran & Formby, 2012). This finding was reflected in a number of tasks conducted in this thesis, although on some tasks the WS group performed below the level of non-verbal ability of the youngest TD group, or with a different pattern of performance to TD children.

The findings from the experimental work presented here provide insight into the specific impairments that adolescent and adult individuals with WS have on a variety of spatial tasks, and the types of spatial mental representations used during large-scale navigation in this group. Studies examining the developmental course of visuospatial abilities in WS typically indicate that cognitive measures are better predictors of developmental progression than chronological age in this group (J. Atkinson et al., 2006; Nardini et al., 2008). In studies 1 and 2 however, a large age-range in the WS group was used and age-related changes were observed in WS on the OB mental rotation task (study 1). This finding may be indicative of plasticity even in the adult WS brain, a time in development that is often noted as remaining relatively unchanging in the level of cognitive functioning in WS (Howlin et al., 2010). However, the inclusion of such a wide age-range in the WS group may have resulted in variability in this group that was more related to task-related difficulties in the youngest and oldest individuals such as understanding the task or associated motor requirements. Therefore, as a precautionary measure in study 4, the age range of the WS group was truncated relative to the

previous studies to account for this. Although individual differences were still be expected in the WS group in study 4, these may have related more to variability in level of cognitive functioning.

Despite the limited changes with age in adults with WS, the dynamic nature of development and brain plasticity during the early years suggests that there may be profound changes throughout development in the extent to which different visuospatial abilities are divergent in WS. Moreover, as mentioned earlier, there are likely to be changing influences of genetic deletions on the visuospatial phenotype over development at different levels of functioning (for example; metabolic, cortical, and behavioural) (Karmiloff-Smith, 2006; Osborne, 2012; Scerif & Karmiloff-Smith, 2005). To examine developmental changes in visuospatial abilities in WS and not just the 'end-point' level of ability in adulthood, future research would benefit from more longitudinal, developmental designs (Thomas, Purser, & Van Herwegen, 2012) in order to examine how these processes develop, and why this may result in specific impairments.

A primary focus of this research was in the changes with age across TD groups in the ability to use different navigation strategies and to switch successfully between spatial frames of reference. As this is not considered a linear process, but occurs within a short timeframe, trajectory analysis would not have been appropriate in this instance and group comparisons were therefore conducted. Further to this, adults with WS were at the level of the youngest TD group (5 or 6 year-olds) in studies 1 and 2 (albeit presenting with a different pattern of performance on some tasks), and even performed at floor-level on some measures. Therefore, the inclusion of children with WS in these studies would not have been additionally informative. Equally, the fine-motor demands of the VE tasks would not have allowed for the TD range to be extended younger than 5 years of age. The inclusion of children with WS on measures of visual-matching (e.g., in study 4), however, may provide insight into the developmental trajectory of this ability in WS. For instance, it is not clear from the current study whether children with WS are similarly able to use a visual-matching strategy to support navigation in the same way as adults with WS. It would also be informative to examine changes in the

pattern of errors and strategies on similar tasks from childhood to adulthood in WS. That said, a linear development of these abilities would not be anticipated, and so would not necessarily benefit from a trajectory analysis.

The use of group comparisons throughout this thesis therefore provided insight into the changes in TD children between 5 and 10 years of age in the types of strategies used to navigate through large-scale environments. The level of ability in adults with WS compared to TD children was also easily examined using this approach. Such group comparisons also demonstrated where navigation strategies were atypical based on what could be expected for the level of verbal and non-verbal ability in WS. That said, there is scope for future research to investigate the emergence of visuospatial abilities in this neurodevelopmental disorder in order to better understand the syndrome-specific pattern of impairments.

Counter to the strengths of using a matching approach such as that indicated throughout this thesis, the comparison of adults with WS to TD children on these spatial navigation tasks has potential limitations. As mentioned in 1.2.1, current theories advocate the role of experience in the development of spatial knowledge, both at an ontogenetic and microgenetic level. As such the comparison of adults and children, who have differing levels of navigational experience may have connotations for the interpretation of some results. Therefore, the inclusion of a second adult developmental disorder group (e.g., Down syndrome or adults with ASD) in a cross-syndrome comparison approach may have provided important insight into the role of age in the development of such spatial abilities in atypical groups. Indeed, if performance across the two atypical groups of comparable chronological age and intellectual (particularly non-verbal) ability is found to be divergent, this would suggest that the specific spatial abilities examined here are not solely attributable to general intellectual ability or age, but indicative of different, syndrome-specific constraints on development.

7.5.3 Using virtual environments (VEs) to examine spatial knowledge

As discussed in section 1.6, there are great advantages to employing the use of VEs to examine large-scale spatial knowledge both in typically developing children and

individuals with developmental disorders. This is particularly so regarding the attainment of extensive experience in an environment and the prospect of manipulating the environment to maintain a consistent experience for each experimental participant. Research suggests that VEs may be suitable equivalents to real world environments (Richardson et al., 1999), with shared neural activity associated with learning in both conditions (Mellet et al., 2010). That said, there are potential limitations to using VEs to approximate real world navigational experience. Firstly, in the real world, there exist greater attentional demands that may have implications for generalising some of the findings presented in this thesis to navigational strategies that would be employed within a naturalistic setting. This may be so for the findings that suggest a reliance on visual matching in WS, when other navigation strategies are not available to them. It is not clear whether in a real-world environment, the more extensive number of multisensory distracters, may have a negative impact on the ability of individuals with WS to use such a strategy. For instance, Péruch and Gaunet (1998) assert that VEs do not support naturalistic interactions between the sensorimotor systems.

Secondly, as mentioned previously, navigation in the real world involves translating and updating between egocentric and allocentric frames of reference (e.g., Vann et al., 2009), and proprioceptive feedback following actual movements through the environment (Ekstrom, 2010; Maguire et al., 1999). Although VEs provide real-time interactivity with an environment and greater subjective feeling of immersion compared viewing static images of environmental locations along a route, the extent to which VEs result in the same level of cognitive processing is questionable. However, it should be noted that within the VEs presented throughout this thesis, a number of participants (particularly TD 8 and 10 year-olds) were able to develop a holistic spatial representation of the environment that may approximate the knowledge acquired from traversing in a real environment. This suggests that such VEs may be suitable measures of investigation into navigational strategies, particularly when used as complementary to real-world navigational studies.

7.6 Implications of results for individuals with WS

7.6.1 Everyday living

Difficulties in mentally rotating objects or the self in WS, as reported in study 1, suggest that everyday tasks that require this aspect of spatial processing; for example, setting a table from a single viewpoint, would be problematic. Importantly, in relation to large-scale spatial abilities, impaired mental rotation has an impact on the specific remediation strategies that can be used for individuals with WS during navigation. For example, the use of maps that require the navigator to mentally transform the spatial information from a table-top viewpoint into the first-person perspective, is likely to be particularly challenging (e.g., Farran et al., 2010).

The findings presented in studies 2 and 4 inform our understanding of not only the impairments individuals with WS demonstrate on large-scale spatial tasks, but also some of the navigational strategies predominantly employed by individuals in this group. Without the time and physical constraints imposed by learning in a real-world environment, the use of VEs demonstrated how individuals with WS are able to learn to make appropriate responses at decision points along a route. Relative strengths in learning a fixed route and a reliance on visual matching in order to successfully learn and retrace such a route may have profound implications for learning to navigate independently and for quality of life. That is, the need to take a detour or getting lost would be particularly problematic as complex navigation strategies are challenging for individuals with WS. Given a reliance on visual matching for navigation, individuals with WS would need to learn the appropriate action to take at each individual decision point along a route. This would certainly be more arduous than the use of other navigation strategies, although points towards a focus for training in WS. For instance, the use of verbal strategies may be used to support sequential organisation of route and landmark information, akin to the use of Aboriginal song-lines for navigation (Norris & Harney, in press).

Even with extended experience in an environment, the findings in this thesis indicate that individuals with WS are unlikely to develop a holistic mental

representation of an environment. Furthermore, an impairment in the ability to switch between an egocentric and allocentric perspective in order to mentally update one's position along a route would also have implications for reorienting one's self after getting lost, or trying to reach one's goal from a different starting place. Difficulties with such tasks are likely to have a profound impact on levels of confidence. Similarly, an impaired ability to relocate one's self following an incorrect turn would increase levels of anxiety for independent travel, which are already reportedly higher in WS than in the typical population (Leyfer, Woodruff-Borden, & Mervis, 2009).

7.6.2 Training and intervention in WS

Given the level of impairment in large-scale spatial navigation in WS, the need to devise suitable methods of training and intervention for individuals with this disorder is vital. The use of VEs to examine spatial abilities in this group was demonstrated to be a useful tool; however, the extent to which such devices can be used for training was not approached in this thesis. That said, the finding that individuals with WS are able to learn a route using a visual-matching strategy implies that VEs that are designed to be representative of real-world routes could be a valuable method of developing familiarity with a given environment and knowledge of the responses that need to be made at certain decision points. Training in VEs that are equivalent to real-world spaces in typical adults (Rose et al., 2000; Wallet et al., 2009) and in individuals with physical disabilities (Foreman et al., 2003; Wilson et al., 1996) has been found to transfer successfully to the real world. However, little is known about whether there would be an equivalent transfer of spatial information from virtual to real space in individuals with intellectual difficulties. This is particularly so considering the additional distractors that would be present in the real world.

The use of interactive web mapping technology that can be easily accessed at home and provides a street-view perspective (for example, Google Maps) could be a useful resource for parents of individuals with WS to point out key landmarks along a route, and for teaching individuals with WS to associate a response with a specific

location. Although the use of such methods would not result in individuals with WS developing a 'cognitive map' or advanced relational knowledge of the environment, they may help to alleviate some of the anxiety related to learning their way around a new place such as a school (using a VE) or a route to the shops (using Google Maps). Similarly, the use of smartphone apps that inform the navigator of the required direction of movement in real-time as well as provide metric and distance information could be particularly beneficial to individuals with WS.

Examining the use of such methods may be an interesting possibility for future research. Further to this, as mentioned above, an advanced understanding of the way in which visuospatial difficulties develop in WS by examining impairments at the level of gene expression, brain, cognition and behaviour across development would further inform our understanding of early interventions that may help remediate some deficits, or at least allow for the training of alternative navigation strategies.

7.7 Future research

Some avenues for future research have already been referred to above. For example, using neuroimaging to examine the specific neural correlates of large-scale navigation in WS compared to TD controls. In particular, future research should examine the extent to which hippocampal and associated regions are involved in processing environmental information in WS compared to TD children and adults. Given that a few individuals with WS were able to use an allocentric spatial frame of reference, does this depend on the integrity of the hippocampus and retrosplenial cortex in the same way as it does in typical adults? Future research would also require a more detailed examination of the neural correlates of different cognitive processes and sub-processes involved in spatial navigation within a typical developmental framework. It may be that there are changes in the cortical regions that subserve spatial processing from childhood to adulthood, even in typical development. Indeed, different networks of activation have been reported in TD children compared to adults during other cognitive tasks such as numerical processing (e.g., Ansari, Garcia, Lucas, Hamon, &

Dhital, 2005). These findings would have important implications for understanding atypical development and neural correlates of spatial processing in WS.

Different patterns of performance between individuals with WS and TD children were reported within this thesis, highlighting specific areas of atypical spatial functioning. For instance, the detriment on 180° trials on OB rotation was only evident in the WS group, showing that unlike TD children they did not use an alternative strategy to perform these tasks. On VPT, the WS group errors were predominantly egocentric compared to the left-right reversal errors in TD groups. Furthermore, on large-scale tasks, the WS group primarily relied on a mixed strategy to navigate and seemed to depend on the presence of landmarks to a greater extent than TD children. Further examination into the specific pattern of performance in WS compared to TD is therefore important. This would help delineate whether some visuospatial deficits in this disorder cannot simply be attributed to poor level of non-verbal ability. The use of eye-tracking technology would greatly enhance this work to identify diverse patterns of behaviour in this disorder. This would be of particular use during large-scale VE navigation tasks, to examine the specific environmental features attended to and gaze patterns in WS compared to TD individuals.

A question not answerable from the present studies, is whether the pattern of large-scale spatial processing shown in WS would also be observed in other neurodevelopmental disorders, particularly in individuals of comparable general intellectual ability. Given the previous discussion about difficulties in linking individual genes to higher-level cognitive functions, the specific genetic origin of WS does not necessarily suggest that the pattern of deficits presented is syndrome-specific. As mentioned in 7.5.2, cross-syndrome comparisons would therefore provide another important addition to the work carried out here. For instance, comparing the pattern of performance and particular strategies used in WS compared to individuals with Down syndrome and ASD would highlight whether atypical processing on these navigation tasks are specific to WS or a hallmark of atypical development in general.

7.8 Summary and concluding remarks

The experimental studies presented in this thesis comprised two main strands of investigation. The experimental work presented here, firstly provides insight into the changes with maturation that drive the use of more complex navigation strategies in typical development. Secondly, the research in this thesis informs our understanding of the specific large-scale visuospatial difficulties and predominant navigation strategies used in individuals with WS. These studies highlight the nature of large-scale spatial deficits in this disorder at the level of behaviour, and the genetic contributions to the WS visuospatial profile. Together, these findings provide insight both into the dynamic nature of visuospatial cognition, and the atypical visuospatial phenotype in WS.

In TD children, improvements in performance on both small- and large-scale spatial tasks were seen between 6 and 8 years of age, with an adult-like pattern of performance occurring by 10 years of age on many tasks. This advanced level of performance with development was attributed to the emergence of the ability to successfully translate between different spatial frames of reference. In particular this referred to the ability to continuously update an egocentric representation of the self (involving viewpoint-dependent information about the direction of required movements) within an allocentric frame of reference (involving an understanding of the viewpoint-independent relationships between locations in an environment). This is in line with the maturation of cortical areas that subserve these types of spatial processing, reported in neuroimaging research (Gogtay et al., 2006; Pine et al., 2002). Measures of the ability to manipulate and transform a mental representation of objects or the self were used to examine underlying processes associated with large-scale navigation abilities. Reliable correlations were only seen in TD 10 year-olds, suggesting that there may be different processes underlying performance at different spatial scales in younger TD children and individuals with WS. The divergent effects of genetic deletions within the WS critical region (WSCR) on different components of visuospatial ability also demonstrated the fractionated nature of visuospatial cognition. An in-depth phenotyping of the visuospatial domain from small- and large-scale tasks spoke of the significance of the genes at the telomeric end of the WSCR – particularly the general transcription factors –

and their effects on the WS profile. For instance, although the preservation of most GTF genes were associated with a high level of navigation ability (albeit with atypical features) in one individual, a contrasting deletion of these telomeric genes in another case did not result in impaired small-scale mental transformation abilities. This study provided insight into the combinatorial and dynamic role of the genes within the WSCR, emphasising in particular the complex nature of the search for direct genotype-phenotype mappings. Moreover, these findings highlight the need to examine the effects of genetic deletions over development and the interaction between genes, brain and environment on the resulting WS cognitive phenotype.

Individuals with WS demonstrated profound impairments in spatial processing at different spatial scales. However, the studies presented in this thesis are indicative of a particular pattern of relative strengths and weaknesses in WS within the visuospatial domain. Although individuals with WS demonstrated impaired allocentric processing, and difficulties with some elements of coding spatial information using an egocentric frame of reference, group performances showed an ability to learn a route in line with level of non-verbal ability. In addition, individuals with WS demonstrated an atypical reliance on an egocentric association-response strategy of visual-matching to successfully learn a route and for subsequent way-finding. This has important implications for navigation in WS. Navigation in daily life rarely requires the use of short-cuts or taking novel routes, but instead predominantly consists of retracing familiar routes to and from school or work and other salient locations. These findings therefore suggest that when navigating through routes that have few distinguishing visual features (e.g., school corridors), or when a change occurs in the environment such as the removal of a key landmark, this is likely to have a profound impact on the daily navigational tasks in individuals with WS.

The nature of visuospatial cognition is dynamic and multifaceted. The pattern of impairments within this domain in individuals with WS, particularly with reference to large-scale navigation abilities, is reflective of this complexity. From the findings in this thesis, some conclusions can be drawn regarding the types of intervention techniques that could alleviate some large-scale navigation difficulties in WS. However,

more research is needed to delineate the genetic and neural underpinnings of visuospatial cognition even within typical development before more targeted and earlier interventions and training approaches can be proposed in WS. The use of a multidisciplinary approach to examining visuospatial cognition and within a developmental framework in future research would therefore further compliment the findings presented in this thesis.

8. Glossary of Terms

Array comparative genome hybridisation (arrayCGH): A technology for the rapid detection of DNA sequence copy number changes (amplifications and deletions) across the entire genome at high resolution. The procedure also allows for simultaneous mapping of these sites within the genomic sequence (Yagihashi et al., 2014).

Allocentric: A representation of space encoded relative to an external frame of reference and the object-to-object relationships within the environment. These representations involve defining the location of an object relative to other objects and are therefore environment- or object-centred.

Centromeric/centromere: The section of DNA that occurs towards/at the point where each half of the chromosome join during mitosis.

***CYLN2/ CLIP2* gene:** A gene within the WSCR that codes for the membrane-microtubule interacting proteins that are found in neurons of the hippocampus, piriform cortex, olfactory bulb and inferior olive (Schubert, 2009).

Egocentric: A representation of space or the location of objects encoded in relation to a body-based frame of reference. These representations involve an understanding of self-to-object relationships based on a body-centred coordinate system.

Elastin (*ELN*) gene: A gene located within the WSCR that codes for proteins rich in hydrophobic amino acids, the deletion and mutations of which cause SVAS, hypertension and soft-tissue changes (Pober, 2010). Haploinsufficiency for one *ELN* gene is the basis for a genetic diagnosis of WS.

Environmental frame of reference: An allocentric spatial frame of reference that is based on the relationships between locations within an environment. For instance, during a task where participants are moved around an array (e.g., Nardini et al., 2006), they are not able to use a body-based frame of reference, or a frame of reference intrinsic to the array, but must use their knowledge of spatial relationships between the array and features within the surrounding environment.

Fluorescence *in-situ* hybridisation (FISH) test: A specialised chromosome analysis technique that uses a DNA probe for the elastin gene and is the standard method for genetically diagnosing WS (Metcalfe, 2012).

General transcription factors (GTFs): (e.g., *GTF2I, GTF2IRD1,* and *GTF2IRD2*). A family of genes that are located at the telomeric end of the WSCR, which code for proteins that act as transcriptional activators and/or repressors. They are thought to have diverse effects on the expression of other genes (Hinsley et al., 2004; Osborne, 2012).

Haploinsufficiency: Only a single functional copy (one allele) of a gene exists, and where the result is a reduction of gene function (only half the gene product is produced leading to insufficient function). It is related to hemizygosity.

Hemizygosity: The state of having only one of a pair of alleles transmitting a specific character.

Intrinsic frame of reference: An allocentric frame of reference centred on an array of objects, such as the specific layout and shape of an array. This is needed to solve tasks in which only an array moves and body-based and environment-based coordinates remain fixed (e.g., Nardini et al., 2006).

Lim domain kinase 1 (*LIMK1*): A gene that is located near the centre of the WSCR that belongs to a protein kinase family involved in brain development, and may play a role in synapse formation and maintenance (Scott & Olson, 2007).

Low-copy repeat (LCR) blocks: Duplicated blocks of repetitive sequences of genomic DNA. Deletions in WS arise as a consequence of misalignment of these repetitive sequences during meiosis (due to the high similarity of the LCRs) (Schubert, 2009).

Megabase (Mb) pairs: A unit of length of nucleic acids (equal to one million base pairs).

Object-based (OB) mental rotation: Tasks that involve imagining what an object would look like from a different orientation, without the need for actual movement. The mental transformation of the location or position of an object or array of objects is conducted relative to a fixed object- or environment-centred spatial frame of reference.

Single copy gene region: The region within the WSCR between the low-copy repeat blocks C mid and B mid and spans a region of ~1.2Mb.

Spatial frame of reference (FoR): The coordinate systems used to encode where things are located in space.

'Sequential egocentric' strategy: The understanding of the temporal order of relationships between the self and decision-points within an environment; for example, the order of body-turns (left-right) to reach a particular location. Thus, these body-based representations or egocentric frames of reference are used in navigation that involves

understanding the temporal, sequential order of movement along a route (Iglói et al., 2009; Rondi-Reig, Petit, Arelo, & Burguiere, 2005).

Supravalvular aortic stenosis (SVAS): A heart defect associated with WS and caused by mutations or deletions of the elastin gene. It results in the narrowing of the large blood vessel (just above the aortic valve) that carries blood from the heart to the rest of the body.

Telomeric/telomere: The segment of DNA that occurs towards/at the end of a chromosome.

Viewpoint-dependent representation: The use of a coordinate system that is based on the observer's particular viewpoint such as a 'mental snap-shot' of a scene. Recall of the layout can only be done using the same viewpoint as time of encoding. This relies on the use of an egocentric reference frame.

Viewpoint-independent representation: The use of a coordinate system based on the external environment or objects within an array that takes into consideration the spatial relationships between places within an environment. For example, a cognitive map would be considered viewpoint independent, i.e. uses an allocentric reference frame.

Visual perspective-taking (VPT): Tasks that involve imagining what a scene would look like from an alternative viewpoint or perspective, without the need for actual movement. The mental transformation of the location or position of the self is conducted relative to a fixed allocentric spatial frame of reference.

Williams syndrome critical region (WSCR): The region on chromosome 7q11.23 that is commonly deleted in WS, spanning 1.55 Mb (~95% of cases) to 1.84 Mb (~5% of cases) of genomic DNA.

9. References

Acredolo, L. P. (1978). Development of spatial orientation in infancy. *Developmental Psychology, 14*, 224-234.

Acredolo, L. P., Adams, A., & Goodwyn, S. W. (1984). The role of self-produced movement and visual tracking in infant spatial orientation. *Journal of Experimental Child Psychology, 38*(2), 312-327. doi: 10.1016/0022-0965(84)90128-0

Allen, G. L., Kirasic, K. C., Dobson, S. H., Long, R. G., & Beck, S. (1996). Predicting environmental learning from spatial abilities: an indirect route. *Intelligence, 22*, 327-355. doi: 10.1016/S0160-2896(96)90026-4

Allen, G. L., Kirasic, K. C., Siegel, A. W., & Herman, J. F. (1979). Developmental issues in cognitive mapping: the selection and utilization of environmental landmarks. *Child Development, 50*(4), 1062-1070. doi: 10.2307/1129332

Allen, G. L., & Ondracek, P. J. (1995). Age-sensitive cognitive abilities related to children's acquisition of spatial knowledge. *Developmental Psychology, 31*(6), 934-945. doi: 10.1037/0012-1649.31.6.934

Amorim, M. A., & Stucchi, N. (1997). Viewer- and object-centered mental explorations of an imagined environment are not equivalent. *Cognitive Brain Research, 5*(3), 229-239. doi: 10.1016/S0926-6410(96)00073-0

Anooshian, L. J., & Nelson, S. K. (1987). Children's knowledge of directional relationships within their neighborhood. *Cognitive Development, 2*(2), 113-126. doi: 10.1016/S0885-2014(87)90098-0

Anooshian, L. J., & Young, D. (1981). Developmental changes in cognitive maps of a familiar neighborhood. *Child Development, 52*(1), 341-348. doi: 10.2307/1129248

Ansari, D., Donlan, C., & Karmiloff-Smith, A. (2007). Typical and atypical development of visual estimation abilities. *Cortex, 43*(6), 758-768. doi: 10.1016/S0010-9452(08)70504-5

Ansari, D., Garcia, N., Lucas, E., Hamon, K., & Dhital, B. (2005). Neural correlates of symbolic number processing in children and adults. *Neuroreport, 16*(16), 1769-1773.

Antonell, A., Del Campo, M., Magano, L. F., Kaufmann, L., de la Iglesia, J. M., Gallastegui, F., . . . Perez-Jurado, L. A. (2010). Partial 7q11.23 deletions further implicate GTF2I and GTF2IRD1 as the main genes responsible for the Williams-Beuren syndrome neurocognitive profile. *Journal of Medical Genetics, 47*(5), 312-320. doi: 10.1136/jmg.2009.071712

Arnold, R., Yule, W., & Martin, N. (1985). The psychological characteristics of infantile hypercalcaemia: a preliminary investigation. *Developmental Medicine and Child Neurology, 27*(1), 49-59. doi: 10.1111/j.1469-8749.1985.tb04524.x

Atkinson, J., Anker, S., Braddick, O., Nokes, L., Mason, A., & Braddick, F. (2001). Visual and visuospatial development in young children with Williams syndrome. *Developmental Medicine and Child Neurology, 43*(5), 330-337. doi: 10.1111/j.1469-8749.2001.tb00213.x

Atkinson, J., & Braddick, O. (2011). From genes to brain development to phenotypic behavior: "dorsal-stream vulnerability" in relation to spatial cognition, attention, and planning of actions in Williams syndrome (WS) and other developmental disorders. *Progress in Brain Research, 189*, 261-283. doi: 10.1016/B978-0-444-53884-0.00029-4

Atkinson, J., Braddick, O., Anker, S., Curran, W., Andrew, R., Wattam-Bell, J., & Braddick, F. (2003). Neurobiological models of visuospatial cognition in children with Williams syndrome: Measures of dorsal-stream and frontal function. *Developmental Neuropsychology, 23*(1-2), 139-172. doi: 10.1080/87565641.2003.9651890

Atkinson, J., Braddick, O., Rose, F. E., Searcy, Y. M., Wattam-Bell, J., & Bellugi, U. (2006). Dorsal-stream motion processing deficits persist into adulthood in Williams syndrome. *Neuropsychologia, 44*(5), 828-833. doi: 10.1016/j.neuropsychologia.2005.08.002

Atkinson, J., King, J., Braddick, O., Nokes, L., Anker, S., & Braddick, F. (1997). A specific deficit of dorsal stream function in Williams' syndrome. *Neuroreport, 8*(8), 1919-1922.

Atkinson, R. C., & Shiffrin, R. M. (1968). Human memory: A proposed system and its control processes. In K. W. Spence & J. T. Spence (Eds.), *The psychology of learning and motivation: (Vol. 2) Advances in research and theory*. New York: Academic Press.

Bailey, J. H., & Witmer, B. G. (1994). Learning and Transfer of Spatial Knowledge in a Virtual Environment. *Human Factors and Ergonomics Society Annual Meeting Proceedings, 38*, 1158-1162. doi: 10.1177/154193129403801803

Bayés, M., Magano, L. F., Rivera, N., Flores, R., & Pérez Jurado, L. A. (2003). Mutational mechanisms of Williams-Beuren syndrome deletions. *American Journal of Human Genetics, 73*(1), 131-151. doi: 10.1086/376565

Bellugi, U., Lichtenberger, L., Jones, W., Lai, Z., & St. George, M. (2000). The neurocognitive profile of Williams syndrome: a complex pattern of strengths and weaknesses. *Journal of Cognitive Neuroscience, 12*(supplement 1), 7-29. doi: 10.1162/089892900561959

Bellugi, U., Sabo, H., & Vaid, J. (1988). Spatial deficits in children with Williams syndrome. In J. Stiles-Davis, U. Kritchevshi, & U. Bellugi (Eds.), *Spatial Cognition: Brain Bases and Development* (pp. 273-297). Hillsdale (NJ): Lawrence Erlbaum.

Bellugi, U., Wang, P. P., & Jernigan, T. L. (1994). Williams syndrome: An unusual neuropsychological profile. In S. H. Broman & J. Grafman (Eds.), *Atypical Cognitive Deficits in Developmental Disorders: Implications for Brain Function* (pp. 23-56). Hillsdale, NJ: Lawrence Erlbaum.

Bernardino, I., Mouga, S., Castelo-Branco, M., & van Asselen, M. (2013). Egocentric and allocentric spatial representations in Williams syndrome. *Journal of the International Neuropsychological Society, 19*(1), 54-62. doi: 10.1017/S1355617712000963

Billinghurst, M., & Weghorst, S. (1995, 11-15 Mar 1995). *The use of sketch maps to measure cognitive maps of virtual environments.* Paper presented at the Virtual Reality Annual International Symposium, 1995. Proceedings.

Boccia, M., Nemmi, F., & Guariglia, C. (2014). Neuropsychology of Environmental Navigation in Humans: Review and Meta-Analysis of fMRI Studies in Healthy Participants. *Neuropsychology Review, 24*(2), 236-251. doi: 10.1007/s11065-014-9247-8

Boddaert, N., Mochel, F., Meresse, I., Seidenwurm, D., Cachia, A., Brunelle, F., . . . Zilbovicius, M. (2006). Parieto-occipital grey matter abnormalities in children with Williams syndrome. *NeuroImage, 30*(3), 721-725. doi: 10.1016/j.neuroimage.2005.10.051

Bolhuis, J. J., & van Kampen, H. S. (1988). Serial position curves in spatial memory of rats: Primacy and recency effects. *The Quarterly Journal of Experimental Psychology Section B, 40*(2), 135-149. doi: 10.1080/14640748808402314

Braddick, O., Atkinson, J., & Wattam-Bell, J. (2003). Normal and anomalous development of visual motion processing: motion coherence and 'dorsal-stream vulnerability'. *Neuropsychologia, 41*(13), 1769-1784. doi: 10.1016/S0028-3932(03)00178-7

Bremner, A. J., Bryant, P. E., & Mareschal, D. (2006). Object-centred spatial reference in 4-month-old infants. *Infant Behavior & Development 29*(1), 1-10. doi: 10.1016/j.infbeh.2005.06.003

Broadbent, H. J., Farran, E. K., & Tolmie, A. (2014). Egocentric and allocentric navigation strategies in Williams syndrome and typical development. *Developmental Science*. doi: 10.1111/desc.12176

Bruno, E., Rossi, N., Thüer, O., Córdoba, R., & Alday, L. E. (2003). Cardiovascular findings, and clinical course, in patients with Williams syndrome. *Cardiology in the Young, 13*(06), 532-536.

Brunyé, T., & Taylor, H. A. (2008). Extended experience benefits spatial mental model development with route but not survey descriptions. *Acta Psychologica, 127*(2), 340-354. doi: 10.1016/j.actpsy.2007.07.002

Bryant, K. J. (1982). Personality correlates of sense of direction and geographical orientation. *Journal of Personality and Social Psychology, 43*, 1318-1324.

Bullens, J., Iglói, K., Berthoz, A., Postma, A., & Rondi-Reig, L. (2010). Developmental time course of the acquisition of sequential egocentric and allocentric navigation strategies. *Journal of Experimental Child Psychology, 107*(3), 337-350. doi: 10.1016/j.jecp.2010.05.010

Bullens, J., Nardini, M., Doeller, C. F., Braddick, O., Postma, A., & Burgess, N. (2010). The role of landmarks and boundaries in the development of spatial memory. *Developmental Science, 13*(1), 170-180. doi: 10.1111/j.1467-7687.2009.00870.x

Burgess, N. (2006). Spatial memory: how egocentric and allocentric combine. *Trends in Cognitive Sciences, 10*(12), 551-557. doi: 10.1016/j.tics.2006.10.005

Burgess, N. (2008). Spatial cognition and the brain. *Annals of the New York Academy of Sciences, 1124*(1), 77-97. doi: 10.1196/annals.1440.002

Burgess, N., Becker, S., King, J. A., & O'Keefe, J. (2001). Memory for events and their spatial context: models and experiments. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 356*(1413), 1493-1503.

Burgess, N., Jeffery, K. J., & O'Keefe, J. (Eds.). (1999). *The hippocampal and parietal foundations of spatial cognition*. Oxford: Oxford University Press.

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron, 35*(4), 625-641. doi: 10.1016/S0896-6273(02)00830-9

Burgess, N., Maguire, E. A., Spiers, H. J., & O'Keefe, J. (2001). A temporoparietal and prefrontal network for retrieving the spatial context of lifelike events. *Neuroimage, 14*(2), 439-453. doi: 10.1006/nimg.2001.0806

Burgess, N., Spiers, H. J., & Paleologou, E. (2004). Orientational manoeuvres in the dark: dissociating allocentric and egocentric influences on spatial memory. *Cognition, 94*(2), 149-166. doi: 10.1016/j.cognition.2004.01.001

Burwell, R. D., Saddoris, M. P., Bucci, D. J., & Wiig, K. A. (2004). Corticohippocampal contributions to spatial and contextual learning. *Journal of Neuroscience, 24*(15), 3826-3836. doi: 10.1523/jneurosci.0410-04.2004

Bushnell, E. W., McKenzie, B. E., Lawrence, D. A., & Connell, S. (1995). The spatial coding strategies of one-year-old infants in a locomotor search task. *Child Development, 66*(4), 937-958. doi: 10.1111/j.1467-8624.1995.tb00914.x

Byrne, P., Becker, S., & Burgess, N. (2007). Remembering the past and imagining the future: A neural model of spatial memory and imagery. *Psychological Review, 114*(2), 340-375. doi: 10.1037/0033-295x.114.2.340

Carney, D. P., Brown, J. H., & Henry, L. A. (2013). Executive function in Williams and Down syndromes. *Res Dev Disabil, 34*(1), 46-55. doi: 10.1016/j.ridd.2012.07.013

Castelo-Branco, M., Mendes, M., Sebastiao, A. R., Reis, A., Soares, M., Saraiva, J., . . . Silva, E. (2007). Visual phenotype in Williams-Beuren syndrome challenges magnocellular

theories explaining human neurodevelopmental visual cortical disorders. *Journal of Clinical Investigation, 117*(12), 3720-3729. doi: 10.1172/JCI32556

Chiang, M.-C., Reiss, A. L., Lee, A. D., Bellugi, U., Galaburda, A. M., Korenberg, J. R., . . . Thompson, P. M. (2007). 3D pattern of brain abnormalities in Williams syndrome visualized using tensor-based morphometry. *NeuroImage, 36*(4), 1096-1109. doi: 10.1016/j.neuroimage.2007.04.024

Childs, M. K., & Polich, J. M. (1979). Developmental differences in mental rotation. *Journal of Experimental Child Psychology, 27*(2), 339-351. doi: 10.1016/0022-0965(79)90054-7

Chrastil, E. (2013). Neural evidence supports a novel framework for spatial navigation. *Psychonomic Bulletin & Review, 20*(2), 208-227. doi: 10.3758/s13423-012-0351-6

Clements, D. H., & Battista, M. T. (1992). Geometry and spatial reasoning. In D. A. Grouws (Ed.), *Handbook of Research on Mathematics Teaching and Learning* (pp. 420–464). New York: McMillan Publishing Company.

Cohen, R., & Schuepfer, T. (1980). The representation of landmarks and routes. *Child Development, 51*(4), 1065-1071.

Collett, M., & Collett, T. S. (2000). How do insects use path integration for their navigation? *Biological Cybernetics, 83*, 245-259.

Committeri, G., Galati, G., Paradis, A. L., Pizzamiglio, L., Berthoz, A., & LeBihan, D. (2004). Reference frames for spatial cognition: different brain areas are involved in viewer-, object-, and landmark-centered judgments about object location. *Journal of Cognitive Neuroscience, 16*(9), 1517-1535. doi: 10.1162/0898929042568550

Conning, A. M., & Byrne, R. W. (1984). Pointing to preschool children's spatial competence: A study in natural settings. *Journal of Environmental Psychology, 4*(2), 165-175. doi: 10.1016/S0272-4944(84)80032-8

Cornell, E. H., Heth, C. D., & Broda, L. S. (1989). Children's wayfinding: response to instructions to use environmental landmarks. *Developmental Psychology, 25*(5), 755-764.

Costanzo, F., Varuzza, C., Menghini, D., Addona, F., Gianesini, T., & Vicari, S. (2013). Executive functions in intellectual disabilities: a comparison between Williams syndrome and Down syndrome. *Res Dev Disabil, 34*(5), 1770-1780. doi: 10.1016/j.ridd.2013.01.024

Courbois, Y. (2000). The role of stimulus axis salience in children's ability to mentally rotate unfamiliar figures. *The European Journal of Cognitive Psychology, 12*, 261-269.

Courbois, Y., Farran, E. K., Lemahieu, A., Blades, M., Mengue-Topio, H., & Sockeel, P. (2013). Wayfinding behaviour in Down syndrome: A study with virtual environments. *Research in Developmental Disabilities, 34*(5), 1825-1831. doi: 10.1016/j.ridd.2013.02.023

Courbois, Y., Oross, S., & Clerc, J. (2007). Mental rotation of unfamiliar stimuli by teenagers with mental retardation: role of feature salience. *American Journal of Mental Retardation, 112*(5), 311-318. doi: 10.1352/0895-8017(2007)112[0311

Cousins, J. H., Siegel, A. W., & Maxwell, S. E. (1983). Way finding and cognitive mapping in large-scale environments: A test of a developmental model. *Journal of Experimental Child Psychology, 35*(1), 1-20. doi: 10.1016/0022-0965(83)90066-8

Crawford, J. R., Garthwaite, P. H., & Porter, S. (2010). Point and interval estimates of effect sizes for the case-controls design in neuropsychology: rationale, methods, implementations, and proposed reporting standards. *Cognitive Neuropsychology, 27*(3), 245-260. doi: 10.1080/02643294.2010.513967

Crawford, J. R., & Howell, D. C. (1998). Comparing an Individual's Test Score Against Norms Derived from Small Samples. *The Clinical Neuropsychologist, 12*(4), 482-486. doi: 10.1076/clin.12.4.482.7241

Creem, S. H., Downs, T. H., Wraga, M., Harrington, G. S., Proffitt, D. R., & Downs, J. H. (2001). An fMRI study of imagined self-rotation. *Cognition Affect and Behavioural Neuroscience, 1*(3), 239-249.

Curran, M. E., Atkinson, D. L., Ewart, A. K., Morris, C. A., Leppert, M. F., & Keating, M. T. (1993). The elastin gene is disrupted by a translocation associated with supravalvular aortic stenosis. *Cell, 73*(1), 159-168. doi: 10.1016/0092-8674(93)90168-P

Dabbs, J. M., Chang, E. L., Strong, R. A., & Milun, R. (1998). Spatial ability, navigation strategy, and geographic knowledge among men and women. *Evolution and Human Behavior, 19*(2), 89-98. doi: 10.1016/S1090-5138(97)00107-4

Dai, L., Bellugi, U., Chen, X. N., Pulst-Korenberg, A. M., Jarvinen-Pasley, A., Tirosh-Wagner, T., . . . Korenberg, J. R. (2009). Is it Williams syndrome? GTF2IRD1 implicated in visual-spatial construction and GTF2I in sociability revealed by high resolution arrays. *American Journal of Medical Genetics, 149A*(3), 302-314. doi: 10.1002/ajmg.a.32652

Davidson, M. C., Amso, D., Anderson, L. C., & Diamond, A. (2006). Development of cognitive control and executive functions from 4 to 13 years: Evidence from manipulations of memory, inhibition, and task switching. *Neuropsychologia, 44*(11), 2037-2078.

Davies, M., Udwin, O., & Howlin, P. (1998). Adults with Williams syndrome. Preliminary study of social, emotional and behavioural difficulties. *The British Journal of Psychiatry, 172*(3), 273-276.

Davis, G. A., & Hyun, E. (2005). A study of kindergarten children's spatial representation in a mapping project. *Mathematics Education Research Journal, 17*(1), 73-100.

Deruelle, C., Rondan, C., Mancini, J., & Livet, M.-O. (2006). Do children with Williams syndrome fail to process visual configural information? *Research in Developmental Disabilities, 27*(3), 243-253. doi: 10.1016/j.ridd.2005.03.002

Diamond, A. (1990). Developmental Time Course in Human Infants and Infant Monkeys, and the Neural Bases of, Inhibitory Control in Reachinga. *Annals of the New York Academy of Sciences, 608*(1), 637-676.

Doeller, C. F., Barry, C., & Burgess, N. (2010). Evidence for grid cells in a human memory network. *Nature, 463*(7281), 657-661.

Doeller, C. F., King, J. A., & Burgess, N. (2008). Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proceedings of the National Academy of Science USA, 105*(15), 5915-5920.

Donnai, D., & Karmiloff-Smith, A. (2000). Williams syndrome: from genotype through to the cognitive phenotype. *American Journal of Medical Genetics, 97*(2), 164-171. doi: 10.1002/1096-8628(200022)97:2<164::AID-AJMG8>3.0.CO;2-F

Dunn, L. M., Dunn, D. M., Styles, B., & Sewell, J. (2009). The British Picture Vocabulary Scale - 3rd Edition. London: GL Assessment.

Dyer, F. C., Berry, N. A., & Richard, A. S. (1993). Honey bee spatial memory: use of route-based memories after displacement. *Animal Behaviour, 45*, 1028-1030.

Dykens, E. M. (2003). Anxiety, fears, and phobias in persons with Williams syndrome. *Developmental Neuropsychology, 23*(1-2), 291-316. doi: 10.1080/87565641.2003.9651896

Eckert, M. A., Hu, D., Eliez, S., Bellugi, U., Galaburda, A. M., Korenberg, J., . . . Reiss, A. L. (2005). Evidence for superior parietal impairment in Williams syndrome. *Neurology, 64*, 152-153. doi: 10.1212/01.WNL.0000148598.63153.8A

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nature Reviews Neuroscience, 1*(1), 41-50. doi: 10.1038/35036213

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M., & Tanila, H. (1999). The hippocampus, memory, and place cells: is it spatial memory or a memory space? *Neuron, 23*(2), 209-226.

Ekstrom, A. (2010). Navigation in Virutal Space: Psychological and Neural Aspects. In G. F. Koob, M. Le Moal, & R. F. Thompson (Eds.), *Encyclopedia of Behavioral Neuroscience* (Vol. 2, pp. 286-293). Oxford: Academic Press.

Elliott, C. D. (1990). *The Differential Ability Scales*. San Antonio, TX: The Psychological Corporation.

Elliott, C. D., Smith, P., & McCulloch, K. (1996). *British Ability Scales II*. Windsor: NFER-Nelson.

Epley, N., Morewedge, C. K., & Keysar, B. (2004). Perspective taking in children and adults: Equivalent egocentrism but differential correction. *Journal of Experimental Social Psychology, 40*(6), 760-768. doi: 10.1016/j.jesp.2004.02.002

Epstein, R. A. (2008). Parahippocampal and retrosplenial contributions to human spatial navigation. *Trends in Cognitive Sciences, 12*(10), 388-396. doi: 10.1016/j.tics.2008.07.004

Epstein, R. A., & Higgins, J. S. (2007). Differential parahippocampal and retrosplenial involvement in three types of visual scene recognition. *Cerebral Cortex, 17*(7), 1680-1693. doi: 10.1093/cercor/bhl079

Estes, D. (1998). Young children's awareness of their mental activity: the case of mental rotation. *Child Development, 69*(5), 1345-1360. doi: 10.1111/j.1467-8624.1998.tb06216.x

Ewart, A. K., Jin, W., Atkinson, D., Morris, C. A., & Keating, M. T. (1994). Supravalvular aortic stenosis associated with a deletion disrupting the elastin gene. *The Journal of Clinical Investigation, 93*(3), 1071-1077. doi: 10.1172/JCI117057

Farran, E. K., Blades, M., Boucher, J., & Tranter, L. J. (2010). How do individuals with Williams syndrome learn a route in a real-world environment? *Developmental Science, 13*(3), 454-468. doi: 10.1111/j.1467-7687.2009.00894.x

Farran, E. K., Courbois, Y., Van Herwegen, J., & Blades, M. (2012). How useful are landmarks when learning a route in a virtual environment? Evidence from typical development and Williams syndrome. *Journal of Experimental Child Psychology, 111*(4), 571-586. doi: 10.1016/j.jecp.2011.10.009

Farran, E. K., Courbois, Y., Van Herwegen, J., Cruickshank, A. G., & Blades, M. (2012). Colour as an environmental cue when learning a route in a virtual environment: Typical and atypical development. *Research in Developmental Disabilities, 33*(3), 900-908. doi: 10.1016/j.ridd.2011.11.017

Farran, E. K., & Formby, S. C. (2012). Visual perception and visuospatial cognition. In E. K. Farran & A. Karmiloff-Smith (Eds.), *Neurodevelopmental Disorders Across the Lifespan: A Neuroconstructivist Approach*. New York: Oxford University Press.

Farran, E. K., & Jarrold, C. (2003). Visuospatial Cognition in Williams Syndrome: Reviewing and Accounting for the Strengths and Weaknesses in Performance. *Developmental Neuropsychology, 23*(1), 173 - 200. doi: 10.1080/87565641.2003.9651891

Farran, E. K., & Jarrold, C. (2004). Exploring block construction and mental imagery: Evidence of atypical orientation discrimination in Williams syndrome. *Visual Cognition, 11*(8), 1019-1039. doi: 10.1080/13506280444000058b

Farran, E. K., Jarrold, C., & Gathercole, S. E. (2001). Block design performance in the Williams syndrome phenotype: a problem with mental imagery? *Journal of Child Psychology & Psychiatry, 42*(6), 719-728. doi: 10.1111/1469-7610.00768

Farran, E. K., Jarrold, C., & Gathercole, S. E. (2003). Divided attention, selective attention and drawing: processing preferences in Williams syndrome are dependent on the task administered. *Neuropsychologia, 41*(6), 676-687. doi: 10.1016/S0028-3932(02)00219-1

Farrell, M. J., Arnold, P., Pettifer, S., Adams, J., Graham, T., & MacManamon, M. (2003). Transfer of Route Learning From Virtual to Real Environments. *Journal of Experimental Psychology: Applied, 9*(4), 219-227. doi: 10.1037/1076-898X.9.4.219

Fayasse, M., & Thibaut, J. P. (2003). Visuo-constructive impairments in Williams syndrome. *Annee Psychologique, 103*(4), 695-727.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex, 1*(1), 1-47. doi: 10.1093/cercor/1.1.1

Fenner, J., Heathcote, D., & Jerrams-Smith, J. (2000). The development of wayfinding competency: asymmetrical effects of visuo-spatial and verbal ability. *Journal of Environmental Psychology, 20*(2), 165-175. doi: 10.1006/jevp.1999.0162

Ferrero, G. B., Biamino, E., Sorasio, L., Banaudi, E., Peruzzi, L., Forzano, S., . . . Silengo, M. C. (2007). Presenting phenotype and clinical evaluation in a cohort of 22 Williams-Beuren syndrome patients. *European Journal of Medical Genetics, 50*(5), 327-337. doi: 10.1016/j.ejmg.2007.05.005

Field, A. (2009). *Discovering Statistics using SPSS: Third Edition*. UK: Sage Publications Ltd.

Fields, A. W., & Shelton, A. L. (2006). Individual skill differences and large-scale environmental learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 32*(3), 506.

Foo, P., Duchon, A., Warren, W. H., Jr., & Tarr, M. J. (2007). Humans do not switch between path knowledge and landmarks when learning a new environment. *Psychological Research, 71*(3), 240-251. doi: 10.1007/s00426-006-0080-4

Foo, P., Warren, W. H., Duchon, A., & Tarr, M. J. (2005). Do humans integrate routes into a cognitive map? map- versus landmark-based navigation of novel shortcuts. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 31*(2), 195-215. doi: 10.1037/0278-7393.31.2.195

Foreman, N. (2007). Spatial cognition and it's facilitation in special populations. In G. L. Allen (Ed.), *Applied Spatial Cognition: From Research to Cognitive Technology* (pp. 129-176). Mahwah, New Jersey: Lawrence Erlbaum Associates, Inc.

Foreman, N., Stanton, D., Wilson, P., & Duffy, H. (2003). Spatial Knowledge of a Real School Environment Acquired From Virtual or Physical Models by Able-Bodied Children and Children With Physical Disabilities. *Journal of Experimental Psychology: Applied, 9*(2), 67-74. doi: 10.1037/1076-898X.9.2.67

Foster, D. J., & Knierim, J. J. (2012). Sequence learning and the role of the hippocampus in rodent navigation. *Current Opinion in Neurobiology, 22*(2), 294-300. doi: 10.1016/j.conb.2011.12.005

Foti, F., Petrosini, L., Cutuli, D., Menghini, D., Chiarotti, F., Vicari, S., & Mandolesi, L. (2011). Explorative function in Williams syndrome analyzed through a large-scale task with multiple rewards. *Research in Developmental Disabilities, 32*(3), 972-985. doi: 10.1016/j.ridd.2011.02.001

Frangiskakis, J. M., Ewart, A. K., Morris, C. A., Mervis, C. B., Bertrand, J., Robinson, B. F., . . . Keating, M. T. (1996). LIM-kinase1 hemizygosity implicated in impaired visuospatial constructive cognition. *Cell, 86*(1), 59-69. doi: 10.1016/S0092-8674(00)80077-X

Freundschuh, S., & Egenhofer, M. (1997). Human conceptions of spaces: Implications for geographic information systems. *Transactions in GIS, 2*(4), 361-375.

Fusco, C., Micale, L., Augello, B., Teresa Pellico, M., Menghini, D., Alfieri, P., . . . Merla, G. (2013). Smaller and larger deletions of the Williams Beuren syndrome region implicate genes involved in mild facial phenotype, epilepsy and autistic traits. *European Journal of Human Genetics*. doi: 10.1038/ejhg.2013.101

Galati, G., Lobel, E., Vallar, G., Berthoz, A., Pizzamiglio, L., & Le Bihan, D. (2000). The neural basis of egocentric and allocentric coding of space in humans: a functional

magnetic resonance study. *Experimental Brain Research, 133*(2), 156-164. doi: 10.1007/s002210000375

Gärling, T., & Golledge, R. G. (2000). Cognitive mapping and spatial decision-making. In R. Kitchin & S. Freundschuh (Eds.), *Cognitive Mapping: Past, Present, and Future* (pp. 44-65). London & New York: Routledge.

Ghaem, O., Mellet, E., Crivello, F., Tzourio, N., Mazoyer, B., Berthoz, A., & Denis, M. (1997). Mental navigation along memorized routes activates the hippocampus, precuneus, and insula. *NeuroReport, 8*(3), 739-744.

Ghetti, S., DeMaster, D. M., Yonelinas, A. P., & Bunge, S. A. (2010). Developmental differences in medial temporal lobe function during memory encoding. *Journal of Neuroscience, 30*(28), 9548-9556. doi: 10.1523/jneurosci.3500-09.2010

Gogtay, N., Nugent, T. F., Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., . . . Thompson, P. M. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus, 16*(8), 664-672. doi: 10.1002/hipo.20193

Golledge, R. G., & Spector, A. N. (1978). Comprehending the urban environment: theory and practice. *Geographical Analysis, 10*(4), 403-426. doi: 10.1111/j.1538-4632.1978.tb00667.x

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neuroscience, 15*(1), 20-25.

Gothelf, D., Farber, N., Raveh, E., Apter, A., & Attias, J. (2006). Hyperacusis in Williams syndrome: characteristics and associated neuroaudiologic abnormalities. *Neurology, 66*(3), 390-395. doi: 10.1212/01.wnl.0000196643.35395.5f

Gray, V., Karmiloff-Smith, A., Funnell, E., & Tassabehji, M. (2006). In-depth analysis of spatial cognition in Williams syndrome: A critical assessment of the role of the LIMK1 gene. *Neuropsychologia, 44*(5), 679-685. doi: 10.1016/j.neuropsychologia.2005.08.007

Gzesh, S. M., & Surber, C. F. (1985). Visual Perspective-Taking Skills in Children. *Child Development, 56*(5), 1204-1213.

Hafting, T., Fyhn, M., Molden, S., Moser, M.-B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature, 436*(7052), 801-806. doi: 10.1038/nature03721

Hardwick, D. A., McIntyre, C. W., & Pick, H. L., Jr. (1976). The content and manipulation of cognitive maps in children and adults. *Monographs of the Society for Research in Child Development, 41*(3), 1-55.

Hartley, T., Maguire, E. A., Spiers, H. J., & Burgess, N. (2003). The Well-Worn Route and the Path Less Traveled: Distinct Neural Bases of Route Following and Wayfinding in Humans. *Neuron, 37*(5), 877-888. doi: 10.1016/S0896-6273(03)00095-3

Hazen, N. L. (1982). Spatial exploration and spatial knowledge: Individual and developmental differences in very young children. *Child Development, 53*, 826-833.

Hazen, N. L., Lockman, J. J., & Pick, H. L., Jr. (1978). The Development of Children's Representations of Large-Scale Environments. *Child Development, 49*(3), 623-636.

Hegarty, M., Montello, D. R., Richardson, A. E., Ishikawa, T., & Lovelace, K. (2006). Spatial abilities at different scales: Individual differences in aptitude-test performance and spatial-layout learning. *Intelligence, 34*, 151-176.

Hegarty, M., & Waller, D. (2004). A dissociation between mental rotation and perspective-taking spatial abilities. *Intelligence, 32*(2), 175-191. doi: 10.1016/j.intell.2003.12.001

Hegarty, M., & Waller, D. (2005). Individual differences in spatial abilities. In P. Shah & A. Miyake (Eds.), *Cambridge Handbook of Visuospatial Thinking* (pp. 121-169). Cambridge: Cambridge University Press.

Heller, R., Rauch, A., Lüttgen, S., Schröder, B., & Winterpacht, A. (2003). Partial deletion of the critical 1.5 Mb interval in Williams-Beuren syndrome. *Journal of Medical Genetics, 40*(8), e99. doi: 10.1136/jmg.40.8.e99

Herman, J. F., Shiraki, J. H., & Miller, B. S. (1985). Young children's ability to infer spatial relationships: evidence from a large, familiar environment. *Child Development, 56*(5), 1195-1203.

Hinsley, T. A., Cunliffe, P., Tipney, H. J., Brass, A., & Tassabehji, M. (2004). Comparison of TFII-I gene family members deleted in Williams-Beuren syndrome. *Protein Science, 13*(10), 2588-2599. doi: 10.1110/ps.04747604

Hirai, M., Muramatsu, Y., Mizuno, S., Kurahashi, N., Kurahashi, H., & Nakamura, M. (2013). Developmental changes in mental rotation ability and visual perspective-taking in children and adults with Williams syndrome. *Front Hum Neurosci, 7*, 856. doi: 10.3389/fnhum.2013.00856

Hirota, H., Matsuoka, R., Chen, X. N., Salandanan, L. S., Lincoln, A., Rose, F. E., . . . Korenberg, J. R. (2003). Williams syndrome deficits in visual spatial processing linked to GTF2IRD1 and GTF2I on chromosome 7q11.23. *Genetic Medicine, 5*(4), 311-321. doi: 10.1097/01.GIM.0000076975.10224.67

Hirtle, S. C., & Hudson, J. (1991). Acquisition of spatial knowledge for routes. *Journal of Environmental Psychology, 11*(4), 335-345. doi: 10.1016/S0272-4944(05)80106-9

Hoffman, J. E., Landau, B., & Pagani, B. (2003). Spatial breakdown in spatial construction: Evidence from eye fixations in children with Williams syndrome. *Cognitive Psychology, 46*(3), 260-301. doi: 10.1016/S0010-0285(02)00518-2

Holmes, M. C., & Sholl, M. J. (2005). Allocentric Coding of Object-to-Object Relations in Overlearned and Novel Environments. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 31*(5), 1069-1087.

Hoogenraad, C. C., Koekkoek, B., Akhmanova, A., Krugers, H., Dortland, B., Miedema, M., . . . Galjart, N. (2002). Targeted mutation of Cyln2 in the Williams syndrome critical region links CLIP-115 haploinsufficiency to neurodevelopmental abnormalities in mice. *Nature Genetics, 32*(1), 116-127. doi: 10.1038/ng954

Howlin, P., Elison, S., Udwin, O., & Stinton, C. (2010). Cognitive, Linguistic and Adaptive Functioning in Williams Syndrome: Trajectories from Early to Middle Adulthood. *Journal of Applied Research in Intellectual Disabilities, 23*(4), 322-336.

Howlin, P., & Udwin, O. (2006). Outcome in adult life for people with Williams syndrome--results from a survey of 239 families. *Journal of Intellectual Disability Research, 50*(Pt 2), 151-160. doi: 10.1111/j.1365-2788.2006.00775.x

Hund, A. M., & Minarik, J. L. (2006). Getting From Here to There: Spatial Anxiety, Wayfinding Strategies, Direction Type, and Wayfinding Efficiency. *Spatial Cognition & Computation, 6*(3), 179-201. doi: 10.1207/s15427633scc0603_1

Huttenlocher, J., Newcombe, N., & Sandberg, E. H. (1994). The coding of spatial location in young children. *Cognitive Psychology, 27*(2), 115-147. doi: 10.1006/cogp.1994.1014

Huttenlocher, J., & Presson, C. C. (1973). Mental rotation and the perspective problem. *Cognitive Psychology, 4*(2), 277-299. doi: 10.1016/0010-0285(73)90015-7

Huttenlocher, J., & Presson, C. C. (1979). The coding and transformation of spatial information. *Cognitive Psychology, 11*(3), 375-394.

Iaria, G., Chen, J., Guariglia, C., Ptito, A., & Petrides, M. (2007). Retrosplenial and hippocampal brain regions in human navigation: complementary functional contributions to the formation and use of cognitive maps. *European Journal of Neuroscience, 25*(3), 890-899. doi: 10.1111/j.1460-9568.2007.05371.x

Iaria, G., Petrides, M., Dagher, A., Pike, B., & Bohbot, V. D. (2003). Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *The journal of neuroscience, 23*(13), 5945-5952.

Iglói, K., Doeller, C. F., Berthoz, A., Rondi-Reig, L., & Burgess, N. (2010). Lateralized human hippocampal activity predicts navigation based on sequence or place memory. *Proceedings of the National Academy of Sciences*. doi: 10.1073/pnas.1004243107

Iglói, K., Zaoui, M., Berthoz, A., & Rondi-Reig, L. (2009). Sequential egocentric strategy is acquired as early as allocentric strategy: Parallel acquisition of these two navigation strategies. *Hippocampus, 19*(12), 1199-1211. doi: 10.1002/hipo.20595

Ishikawa, T., & Montello, D. R. (2006). Spatial knowledge acquisition from direct experience in the environment: Individual differences in the development of metric knowledge and the integration of separately learned places. *Cognitive Psychology, 52*(2), 93-129. doi: 10.1016/j.cogpsych.2005.08.003

Ittelson, W. H. (1973). Environment perception and contemporary perceptual theory. In W. H. Ittelson (Ed.), *Environment and cognition*. New York: Seminar.

Jacobs, J., Kahana, M. J., Ekstrom, A. D., Mollison, M. V., & Fried, I. (2010). A sense of direction in human entorhinal cortex. *Proceedings of the National Academy of Sciences, 107*(14), 6487-6492.

Jansen-Osmann, P. (2002). Using desktop virtual environments to investigate the role of landmarks. *Computers in Human Behavior, 18*(4), 427-436. doi: 10.1016/S0747-5632(01)00055-3

Jansen-Osmann, P., & Fuchs, P. (2006). Wayfinding Behavior and Spatial Knowledge of Adults and Children in a Virtual Environment: The Role of Landmarks. *Experimental Psychology, 53*(3), 171-181. doi: 10.1027/1618-3169.53.3.171

Jansen-Osmann, P., & Wiedenbauer, G. (2004). The representation of landmarks and routes in children and adults: A study in a virtual environment. *Journal of Environmental Psychology, 24*(3), 347-357. doi: 10.1016/j.jenvp.2004.08.003

Janzen, G., & Weststeijn, C. G. (2007). Neural representation of object location and route direction: An event-related fMRI study. *Brain Research, 1165*, 116-125. doi: 10.1016/j.brainres.2007.05.074

Jarrold, C., Baddeley, A. D., & Hewes, A. K. (1998). Verbal and nonverbal abilities in the Williams syndrome phenotype: evidence for diverging developmental trajectories. *Journal of Child Psychology and Psychiatry, 39*(4), 511-523. doi: 10.1111/1469-7610.00347

Jarrold, C., Baddeley, A. D., Hewes, A. K., & Phillips, C. (2001). A Longitudinal Assessment of Diverging Verbal and Non-Verbal Abilities in the Williams Syndrome Phenotype. *Cortex, 37*(3), 423-431. doi: 10.1016/S0010-9452(08)70582-3

Jeffery, K. J., & Burgess, N. (2006). A metric for the cognitive map: found at last? *Trends in Cognitive Sciences, 10*(1), 1-3. doi: 10.1016/j.tics.2005.11.002

Johnson, L. B., Comeau, M., & Clarke, K. D. (2001). Hyperacusis in Williams syndrome. *The Journal of Otolaryngology, 30*(2), 90-92.

Jordan, K., Schadow, J., Wuestenberg, T., Heinze, H. J., & Jancke, L. (2004). Different cortical activations for subjects using allocentric or egocentric strategies in a virtual navigation task. *Neuroreport, 15*(1), 135-140.

Kannass, K. N., Plumert, J. M., McDermott, J., Moore, B., & Durich, N. (2004). The role of the physical context in supporting young children's use of spatiotemporal organization in recall. *British Journal of Developmental Psychology, 22*, 59-82.

Kaplan, P., Kirschner, M., Watters, G., & Costa, M. T. (1989). Contractures in patients with Williams syndrome. *Pediatrics, 84*(5), 895-899.

Karmiloff-Smith, A. (2006). The tortuous route from genes to behavior: A neuroconstructivist approach. *Cognitive, Affective, & Behavioral Neuroscience, 6*(1), 9-17. doi: 10.3758/cabn.6.1.9

Karmiloff-Smith, A. (2012). Brain: The neuroconstructivist approach. In E. K. Farran & A. Karmiloff-Smith (Eds.), *Neurodevelopmental Diosrders Across the Lifespan: A Neuroconstructivist Approach*. New York: Oxford University Press Inc.

Karmiloff-Smith, A., Broadbent, H., Farran, E. K., Longhi, E., D'Souza, D., Metcalfe, K., . . . Sansbury, F. (2012). Social cognition in Williams syndrome: genotype/phenotype insights from partial deletion patients. *Frontiers in Psychology, 3*, 168. doi: 10.3389/fpsyg.2012.00168

Karmiloff-Smith, A., Brown, J. H., Grice, S., & Paterson, S. (2003). Dethroning the myth: Cognitive dissociations and innate modularity in Williams syndrome. *Developmental neuropsychology, 23*(1-2), 227-242.

Karmiloff-Smith, A., Grant, J., Berthoud, I., Davies, M., Howlin, P., & Udwin, O. (1997). Language and Williams Syndrome: How Intact Is "Intact"? *Child Development, 68*(2), 246-262. doi: 10.1111/j.1467-8624.1997.tb01938.x

Karmiloff-Smith, A., Grant, J., Ewing, S., Carette, M. J., Metcalfe, K., Donnai, D., . . . Tassabehji, M. (2003). Using case study comparisons to explore genotype-phenotype correlations in Williams-Beuren syndrome. *Journal of Medical Genetics, 40*(2), 136-140. doi: 10.1136/jmg.40.2.136

Karmiloff-Smith, A., Scerif, G., & Thomas, M. (2002). Different approaches to relating genotype to phenotype in developmental disorders. *Developmental psychobiology, 40*(3), 311-322.

Kelly, J. W., & McNamara, T. P. (2010). Reference frames during the acquisition and development of spatial memories. *Cognition, 116*(3), 409-420. doi: 10.1016/j.cognition.2010.06.002

Kesner, R., Measom, M., Forsman, S., & Holbrook, T. (1984). Serial-position curves in rats: Order memory for episodic spatial events. *Animal Learning & Behavior, 12*(4), 378-382. doi: 10.3758/bf03199983

Kessler, K., & Thomson, L. A. (2010). The embodied nature of spatial perspective taking: Embodied transformation versus sensorimotor interference. *Cognition, 114*(1), 72-88. doi: 10.1016/j.cognition.2009.08.015

King, J. A., Burgess, N., Hartley, T., Vargha-Khadem, F., & O'Keefe, J. (2002). Human hippocampus and viewpoint dependence in spatial memory. *Hippocampus, 12*(6), 811-820. doi: 10.1002/hipo.10070

Kippenhan, J. S., Olsen, R. K., Mervis, C. B., Morris, C. A., Kohn, P., Meyer-Lindenberg, A., & Berman, K. F. (2005). Genetic contributions to human gyrification: sulcal morphometry in Williams syndrome. *Journal of Neuroscience, 25*(34), 7840-7846. doi: 10.1523/jneurosci.1722-05.2005

Klatzky, R. (1998). *Allocentric and Egocentric Spatial Representations: Definitions, Distinctions, and Interconnections.* Paper presented at the Spatial Cognition, An Interdisciplinary Approach to Representing and Processing Spatial Knowledge.

Koehler, U., Pabst, B., Pober, B., & Kozel, B. (2014). Clinical utility gene card for: Williams-Beuren Syndrome [7q11.23]. *European Journal of Human Genetics*. doi: 10.1038/ejhg.2014.28

Kosslyn, S. M., DiGirolamo, G. J., Thompson, W. L., & Alpert, N. M. (1998). Mental rotation of objects versus hands: neural mechanisms revealed by positron emission tomography. *Psychophysiology, 35*(2), 151-161.

Kosslyn, S. M., Margolis, J. A., Barrett, A. M., Goldknopf, E. J., & Daly, P. F. (1990). Age Differences in Imagery Abilities. *Child Development, 61*(4), 995-1010. doi: 10.1111/j.1467-8624.1990.tb02837.x

Kosslyn, S. M., Pick, H. L., Jr., & Fariello, G. R. (1974). Cognitive Maps in Children and Men. *Child Development, 45*(3), 707-716.

Kozhevnikov, M., & Hegarty, M. (2001). A dissociation between object manipulation spatial ability and spatial orientation ability. *Mem Cognit, 29*(5), 745-756.

Kozhevnikov, M., Motes, M. A., Rasch, B., & Blajenkova, O. (2006). Perspective-taking vs. mental rotation transformations and how they predict spatial navigation performance. *Applied Cognitive Psychology, 20*(3), 397-417. doi: 10.1002/acp.1192

Kruse, K., Pankau, R., Gosch, A., & Wohlfahrt, K. (1992). Calcium metabolism in Williams-Beuren syndrome. *Journal of Pediatrics, 121*(6), 902-907.

Kuipers, B. (1978). Modelling spatial knowledge. *Cognitive Science, 2*, 129-153.

Kuipers, B. (1982). The 'map in the head' metaphor. *Environment & Behavior, 14*, 202-220.

Kuipers, B., Tecuci, D. G., & Stankiewicz, B. J. (2003). The Skeleton In The Cognitive Map. *Environment and Behavior, 35*(1), 81-106. doi: 10.1177/0013916502238866

Kumaran, D., & Maguire, E. A. (2005). The human hippocampus: cognitive maps or relational memory? *Journal of Neuroscience, 25*(31), 7254-7259. doi: 10.1523/jneurosci.1103-05.2005

Lakusta, L., Dessalegn, B., & Landau, B. (2010). Impaired geometric reorientation caused by genetic defect. *Proceedings of the National Academy of Science USA, 107*(7), 2813-2817. doi: 10.1073/pnas.0909155107

Lambrey, S., Doeller, C. F., Berthoz, A., & Burgess, N. (2012). Imagining Being Somewhere Else: Neural Basis of Changing Perspective in Space. *Cerebral Cortex, 22*(1), 166-174. doi: 10.1093/cercor/bhr101

Landau, B., Gleitman, H., & Spelke, E. (1981). Spatial knowledge and geometric representation in a child blind from birth. *Science, 213*(4513), 1275-1278.

Landau, B., & Hoffman, J. E. (2005). Parallels between spatial cognition and spatial language: Evidence from Williams syndrome. *Journal of Memory and Language, 53*(2), 163-185.

Lee, P. U., & Tversky, B. (2005). Interplay Between Visual and Spatial: The Effect of Landmark Descriptions on Comprehension of Route/Survey Spatial Descriptions. *Spatial Cognition & Computation: An Interdisciplinary Journal, 5*(2), 163 - 185. doi: 10.1207/s15427633scc052&3_4

Lehnung, M., Leplow, B., Haaland, V. O., Mehdorn, M., & Ferstl, R. (2003). Pointing accuracy in children is dependent on age, sex and experience. *Journal of Environmental Psychology, 23*(4), 419-425. doi: 10.1016/S0272-4944(02)00084-1

Leyfer, O., Woodruff-Borden, J., & Mervis, C. B. (2009). Anxiety disorders in children with Williams syndrome, their mothers, and their siblings: Implications for the etiology of anxiety disorders. *Journal of Neurodevelopmental Disorders, 1*(1), 4-14. doi: 10.1007/s11689-009-9003-1

Li, D. Y., Brooke, B., Davis, E. C., Mecham, R. P., Sorensen, L. K., Boak, B. B., . . . Keating, M. T. (1998). Elastin is an essential determinant of arterial morphogenesis. *Nature, 393*(6682), 276-280. doi: 10.1038/30522

Li, D. Y., Toland, A. E., Boak, B. B., Atkinson, D. L., Ensing, G. J., Morris, C. A., & Keating, M. T. (1997). Elastin point mutations cause an obstructive vascular disease, supravalvular aortic stenosis. *Human Molecular Genetics, 6*(7), 1021-1028. doi: 10.1093/hmg/6.7.1021

Lowery, M. C., Morris, C. A., Ewart, A., Brothman, L. J., Zhu, X. L., Leonard, C. O., . . . Brothman, A. R. (1995). Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: evaluation of 235 patients. *American Journal of Human Genetics, 57*(1), 49-53.

Lynch, K. (1960). *The Image of the City*. Cambridge MA: MIT Press.

Maguire, E. A. (2001). The retrosplenial contribution to human navigation: a review of lesion and neuroimaging findings. *Scandinavian Journal of Psychology, 42*(3), 225-238.

Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: A human navigation nework. *Science, 280*, 921-924.

Maguire, E. A., Burgess, N., & O'Keefe, J. (1999). Human spatial navigation: cognitive maps, sexual dimorphism, and neural substrates. *Current Opinion in Neurobiology, 9*(2), 171-177.

Maguire, E. A., Frackowiak, R. S., & Frith, C. D. (1997). Recalling routes around london: activation of the right hippocampus in taxi drivers. *Journal of Neuroscience, 17*(18), 7103-7110.

Malinowski, J. C. (2001). Mental rotation and real-world wayfinding. *Perceptual and Motor Skills, 92*(1), 19-30.

Mandolesi, L., Addona, F., Foti, F., Menghini, D., Petrosini, L., & Vicari, S. (2009). Spatial competences in Williams syndrome: a radial arm maze study. *International Journal of Developmental Neuroscience, 27*(3), 205-213. doi: 10.1016/j.ijdevneu.2009.01.004

Marchette, S. A., Bakker, A., & Shelton, A. L. (2011). Cognitive mappers to creatures of habit: differential engagement of place and response learning mechanisms predicts human navigational behavior. *Journal of Neuroscience, 31*(43), 15264-15268. doi: 10.1523/jneurosci.3634-11.2011

Marmor, G. S. (1975). Development of kinetic images: When does the child first represent movement in mental images? *Cognitive Psychology, 7*(4), 548-559. doi: 10.1016/0010-0285(75)90022-5

Martens, M. A., Wilson, S. J., & Reutens, D. C. (2008). Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry, 49*(6), 576-608. doi: 10.1111/j.1469-7610.2008.01887.x

McNamara, T. P., Rump, B., & Werner, S. (2003). Egocentric and geocentric frames of reference in memory of large-scale space. *Psychonomic Bulletin and Review, 10*(3), 589-595. doi: 10.3758/BF03196519

McNamara, T. P., & Shelton, A. L. (2003). Cognitive maps and the hippocampus. *Trends in Cognitive Sciences, 7*(8), 333-335. doi: 10.1016/S1364-6613(03)00167-0

Mellet, E., Bricogne, S., Tzourio-Mazoyer, N., Ghaëm, O., Petit, L., Zago, L., . . . Denis, M. (2000). Neural Correlates of Topographic Mental Exploration: The Impact of Route

versus Survey Perspective Learning. *Neuroimage, 12*(5), 588-600. doi: 10.1006/nimg.2000.0648

Mellet, E., Laou, L., Petit, L., Zago, L., Mazoyer, B., & Tzourio-Mazoyer, N. (2010). Impact of the virtual reality on the neural representation of an environment. *Human Brain Mapping, 31*(7), 1065-1075. doi: 10.1002/hbm.20917

Meng, X., Lu, X. J., Li, Z. Z., Green, E. D., Massa, H., Trask, B. J., . . . Keating, M. T. (1998). Complete physical map of the common deletion region in Williams syndrome and identification and characterization of three novel genes. *Human Genetics, 103*(5), 590-599. doi: 10.1007/s004390050874

Meng, Y., Zhang, Y., Tregoubov, V., Janus, C., Cruz, L., Jackson, M., . . . Jia, Z. (2002). Abnormal Spine Morphology and Enhanced LTP in LIMK-1 Knockout Mice. *Neuron, 35*(1), 121-133. doi: 10.1016/S0896-6273(02)00758-4

Menghini, D., Addona, F., Costanzo, F., & Vicari, S. (2010). Executive functions in individuals with Williams syndrome. *Journal of Intellectual Disability Research, 54*(5), 418-432. doi: 10.1111/j.1365-2788.2010.01287

Menghini, D., Di Paola, M., Federico, F., Vicari, S., Petrosini, L., Caltagirone, C., & Bozzali, M. (2011). Relationship Between Brain Abnormalities and Cognitive Profile in Williams Syndrome. *Behavior Genetics, 41*(3), 394-402. doi: 10.1007/s10519-010-9419-0

Mengue-Topio, H., Courbois, Y., Farran, E. K., & Sockeel, P. (2010). Route learning and shortcut performance in adults with intellectual disability: A study with virtual environments. *Research in Developmental Disabilities, 32*(1), 345-352. doi: 10.1016/j.ridd.2010.10.014

Merla, G., Ucla, C., Guipponi, M., & Reymond, A. (2002). Identification of additional transcripts in the Williams-Beuren syndrome critical region. *Human Genetics, 110*(5), 429-438. doi: 10.1007/s00439-002-0710-x

Mervis, C. B., Robinson, B. F., & Pani, J. R. (1999). Visuospatial construction. *American Journal of Human Genetics, 65*(5), 1222-1229. doi: 10.1086/302633

Metcalfe, K. (2012). Clinical profile: Diagnosis and prognosis. In E. K. Farran & A. Karmiloff-Smith (Eds.), *Neurodevelopmental Disorders Across the Lifespan: A Neuroconstructivist Approach*. New York: Oxford University Press Inc.

Meyer-Lindenberg, A., Kohn, P., Mervis, C. B., Kippenhan, J. S., Olsen, R. K., Morris, C. A., & Berman, K. F. (2004). Neural Basis of Genetically Determined Visuospatial Construction Deficit in Williams Syndrome. *Neuron, 43*(5), 623-631. doi: 10.1016/j.neuron.2004.08.014

Meyer-Lindenberg, A., Mervis, C. B., & Berman, K. F. (2006). Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. *Nature Reviews Neuroscience, 7*(5), 380-393. doi: 10.1038/nrn1906

Meyer-Lindenberg, A., Mervis, C. B., Sarpal, D., Koch, P., Steele, S., Kohn, P., . . . Berman, K. F. (2005). Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. *Journal of Clinical Investigation, 115*(7), 1888-1895. doi: 10.1172/jci24892

Milner, A. D., & Goodale, M. A. (1995). *The visual brain in action*. Oxford: New York: Oxford University Press.

Moar, I., & Carleton, L. R. (1982). Memory for routes. *Quarterly Journal of Experimental Psychology Section A: Human Experimental Psychology, 34*(3), 381 - 394.

Mobbs, D., Eckert, M. A., Mills, D., Korenberg, J., Bellugi, U., Galaburda, A. M., & Reiss, A. L. (2007). Frontostriatal Dysfunction During Response Inhibition in Williams Syndrome. *Biological Psychiatry, 62*(3), 256-261. doi: 10.1016/j.biopsych.2006.05.041

Moeser, S. D. (1988). Cognitive Mapping in a Complex Building. *Environment and Behavior, 20*(1), 21-49. doi: 10.1177/0013916588201002

Montello, D. R. (1993). Scale and multiple psychologies of space. In A. U. Frank & I. Campari (Eds.), *Spatial Information Theory A Theoretical Basis for GIS* (Vol. 716, pp. 312-321): Springer Berlin Heidelberg.

Montello, D. R. (1998). A new framework for understanding the acquisition of spatial knowledge in large-scale environments. In M. J. Egenhofer & G. Golledge (Eds.),

Spatial and Temporal Reasoning in Geographic Information Systems (pp. 143-154). New York: Oxford University Press.

Montello, D. R., Hegarty, M., Richardson, A. E., & Waller, D. (2004). Spatial memory of real environments, virtual environments, and maps. In G. L. Allen (Ed.), *Human Spatial Memory: Remembering Where* (pp. 251-285). Mahwah, N.J.: Lawrence Erlbaum Associates, Inc.

Montello, D. R., & Pick, H. L. (1993). Integrating knowledge of vertically-aligned large-scale spaces. *Environment & Behavior, 25*, 457-484.

Moraleda, E., Broglio, C., Rodriguez, F., & Gomez, A. (2013). Development of different spatial frames of reference for orientation in small-scale environments. *Psicothema, 25*(4), 468-475. doi: 4139 [pii]
10.7334/psicothema2013.29 [doi]

Morgan, L. K., Macevoy, S. P., Aguirre, G. K., & Epstein, R. A. (2011). Distances between real-world locations are represented in the human hippocampus. *Journal of Neuroscience, 31*(4), 1238-1245. doi: 10.1523/JNEUROSCI.4667-10.2011

Morganti, F., Carassa, A., & Geminiani, G. (2007). Planning optimal paths: A simple assessment of survey spatial knowledge in virtual environments. *Computers in Human Behavior, 23*(4), 1982-1996.

Morris, C. A. (2011). Williams syndrome. In S. B. Cassidy & J. A. Allanson (Eds.), *Management of Genetic Syndromes* (3rd ed.): Wiley-Blackwell.

Morris, C. A., Demsey, S. A., Leonard, C. O., Dilts, C., & Blackburn, B. L. (1988). Natural history of Williams syndrome: Physical characteristics. *The Journal of Pediatrics, 113*(2), 318-326. doi: 10.1016/S0022-3476(88)80272-5

Morris, C. A., & Mervis, C. B. (1999). Williams syndrome. In S. Goldstein & C. Reynolds (Eds.), *Handbook of Neurodevelopmental and Genetic Disorders in Children* (pp. 555-590). New York: Guilford.

Morris, C. A., Mervis, C. B., Hobart, H. H., Gregg, R. G., Bertrand, J., Ensing, G. J., . . . Stock, A. D. (2003). GTF2I hemizygosity implicated in mental retardation in Williams syndrome: Genotype-phenotype analysis of five families with deletions in the Williams

syndrome region. *American Journal of Medical Genetics, 123A*(1), 45-59. doi: 10.1002/ajmg.a.20496

Morris, R. G. M., Garrud, P., Rawlins, J. N. P., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature, 297*(5868), 681-683.

Mou, W., Fan, Y., McNamara, T. P., & Owen, C. B. (2008). Intrinsic frames of reference and egocentric viewpoints in scene recognition. *Cognition, 106*(2), 750-769. doi: 10.1016/j.cognition.2007.04.009

Mou, W., McNamara, T. P., Rump, B., & Xiao, C. (2006). Roles of Egocentric and Allocentric Spatial Representations in Locomotion and Reorientation. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 32*(6), 1274-1290. doi: 10.1037/0278-7393.32.6.1274

Mou, W., McNamara, T. P., Valiquette, C. M., & Rump, B. (2004). Allocentric and egocentric updating of spatial memories. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 30*, 142-157.

Müller, M., & Wehner, R. (1988). Path integration in desert ants, *Cataglyphis fortis*. *Proceedings of the National Academy of Science USA, 85*, 5287-5290.

Murdock, B. B. J. (1962). The serial position effect in free recall. *Journal of Experimental Psychology, 64*, 482-488.

Nadel, L., & Hardt, O. (2004). The spatial brain. *Neuropsychology, 18*, 473-476.

Nakamura, M., Kaneoke, Y., Watanabe, K., & Kakigi, R. (2002). Visual information process in Williams syndrome: intact motion detection accompanied by typical visuospatial dysfunctions. *The European Journal of Neuroscience, 16*(9), 1810-1818. doi: 10.1046/j.1460-9568.2002.02227.x

Nardini, M., Atkinson, J., Braddick, O., & Burgess, N. (2008). Developmental trajectories for spatial frames of reference in Williams syndrome. *Developmental Science, 11*(4), 583-595. doi: 10.1111/j.1467-7687.2007.00662

Nardini, M., Burgess, N., Breckenridge, K., & Atkinson, J. (2006). Differential developmental trajectories for egocentric, environmental and intrinsic frames of reference in spatial memory. *Cognition, 101*(1), 153-172. doi: 10.1016/j.cognition.2005.09.005

Nardini, M., Thomas, R. L., Knowland, V. C., Braddick, O. J., & Atkinson, J. (2009). A viewpoint-independent process for spatial reorientation. *Cognition, 112*(2), 241-248. doi: 10.1016/j.cognition.2009.05.003

Neggers, S. F., Van der Lubbe, R. H., Ramsey, N. F., & Postma, A. (2006). Interactions between ego- and allocentric neuronal representations of space. *NeuroImage, 31*(1), 320-331. doi: 10.1016/j.neuroimage.2005.12.028

Nemmi, F., Boccia, M., Piccardi, L., Galati, G., & Guariglia, C. (2013). Segregation of neural circuits involved in spatial learning in reaching and navigational space. *Neuropsychologia, 51*(8), 1561-1570. doi: 10.1016/j.neuropsychologia.2013.03.031

Newcombe, N., & Frick, A. (2010). Early Education for Spatial Intelligence: Why, What, and How. *Mind, Brain, and Education, 4*(3), 102-111. doi: 10.1111/j.1751-228X.2010.01089.x

Newcombe, N., & Huttenlocher, J. (1992). Children's Early Ability to Solve Perspective-Taking Problems. *Developmental Psychology, 28*(4), 635-643. doi: 10.1037/0012-1649.28.4.635

Newcombe, N., & Huttenlocher, J. (2000). *Making Space: the development of spatial representation and reasoning*. Cambridge, MA: MIT Press.

Newcombe, N., Huttenlocher, J., Drummey, A. B., & Wiley, J. G. (1998). The development of spatial location coding: Place learning and dead reckoning in the second and third years. *Cognitive Development, 13*(2), 185-200. doi: 10.1016/S0885-2014(98)90038-7

Newcombe, N., & Liben, L. S. (1982). Barrier effects in the cognitive maps of children and adults. *Journal of Experimental Child Psychology, 34*(1), 46-58.

Norris, R. P., & Harney, B. Y. (in press). Songlines and navigation in Wardaman and other Aboriginal cultures. *Journal of Astronomical History and Heritage*.

O'Hearn, K., Courtney, S., Street, W., & Landau, B. (2009). Working memory impairment in people with Williams syndrome: effects of delay, task and stimuli. *Brain Cognition, 69*(3), 495-503. doi: 10.1016/j.bandc.2008.10.004

O'Keefe, J., & Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford: Oxford University Press.

Okagaki, L., & Frensch, P. A. (1994). Effects of video game playing on measures of spatial performance: Gender effects in late adolescence. *Journal of Applied Developmental Psychology, 15*(1), 33-58. doi: 10.1016/0193-3973(94)90005-1

Osborne, L. R. (2010). Animal models of Williams syndrome. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 154C*(2), 209-219. doi: 10.1002/ajmg.c.30257

Osborne, L. R. (2012). Genes: The gene expression approach. In E. K. Farran & A. Karmiloff-Smith (Eds.), *Neurodevelopmental Disorders Across the Lifespan: A Neuroconstructivist Approach*. New York: Oxford University Press Inc.

Overman, W. H., Pate, B. J., Moore, K., & Peuster, A. (1996). Ontogeny of Place Learning in Children as Measured in the Radial Arm Maze, Morris Search Task, and Open Field Task. *Behavioral Neuroscience, 110*(6), 1205-1228.

Packard, M. G., & Knowlton, B. J. (2002). Learning and memory functions of the Basal Ganglia. *Annual Review of Neuroscience, 25*(1), 563-593. doi: doi:10.1146/annurev.neuro.25.112701.142937

Packard, M. G., & McGaugh, J. L. (1996). Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiology of learning and memory, 65*(1), 65-72.

Palermo, L., Iaria, G., & Guariglia, C. (2008). Mental imagery skills and topographical orientation in humans: A correlation study. *Behavioural Brain Research, 192*(2), 248-253. doi: 10.1016/j.bbr.2008.04.014

Pani, J. R., Mervis, C. B., & Robinson, B. F. (1999). Global Spatial Organization by Individuals with Williams Syndrome. *Psychological Science, 10*(5), 453-458. doi: 10.1111/1467-9280.00186

Parsons, L. M. (1987). Imagined spatial transformation of one's body. *Journal of Experimental Psychology: General, 116*, 172-191.

Passini, R. (1984). Spatial representations, a wayfinding perspective. *Journal of Environmental Psychology, 4*(2), 153-164. doi: 10.1016/S0272-4944(84)80031-6

Paterson, S. J., Brown, J. H., Gsodl, M. K., Johnson, M. H., & Karmiloff-Smith, A. (1999). Cognitive modularity and genetic disorders. *Science, 286*(5448), 2355-2358. doi: 10.1126/science.286.5448.2355

Pazzaglia, F., & De Beni, R. (2001). Strategies of processing spatial information in survey and landmark-centred individuals. *The European Journal of Cognitive Psychology, 13*, 493-508.

Pazzaglia, F., & De Beni, R. (2006). Are people with high and low mental rotation abilities differently susceptible to the alignment effect? *Perception, 35*(3), 369-383.

Pearson, J. L., & Ialongo, N. S. (1986). The relationship between spatial ability and environmental knowledge. *Journal of Environmental Psychology, 6*(4), 299-304. doi: 10.1016/S0272-4944(86)80003-2

Pellizzer, G., Bâ, M. B., Zanello, A., & Merlo, M. C. G. (2009). Asymmetric learning transfer between imagined viewer- and object-rotations: Evidence of a hierarchical organization of spatial reference frames. *Brain and Cognition, 71*(3), 272-278. doi: 10.1016/j.bandc.2009.08.001

Peoples, R., Franke, Y., Wang, Y. K., Perez-Jurado, L., Paperna, T., Cisco, M., & Francke, U. (2000). A physical map, including a BAC/PAC clone contig, of the Williams-Beuren syndrome--deletion region at 7q11.23. *American Journal of Human Genetics, 66*(1), 47-68. doi: 10.1086/302722

Péruch, P., & Gaunet, F. (1998). Virtual environments as a promising tool for investigating human spatial cognition. *Current Psychology of Cognition, 17*(4-5), 881-899.

Pezzini, G., Vicari, S., Volterra, V., Milani, L., & Ossella, M. T. (1999). Children with williams syndrome: Is there a single neuropsychological profile? *Developmental Neuropsychology, 15*(1), 141-155. doi: 10.1080/87565649909540742

Piaget, J., & Inhelder, B. (1967). *The Child's Conception of Space*. New York: Norton.

Piaget, J., & Inhelder, B. (1971). *Mental Imagery in the Child*. New York: Basic Books.

Pick, H. L. (1972). *Mapping Children - Mapping Space*. Paper presented at the Paper presented at the meeting of the American Psychological Association Honolulu, Hawaii.

Pigott, S., & Milner, B. (1993). Memory for different aspects of complex visual scenes after unilateral temporal- or frontal-lobe resection. *Neuropsychologia, 31*(1), 1-15. doi: 10.1016/0028-3932(93)90076-C

Pine, D. S., Grun, J., Maguire, E. A., Burgess, N., Zarahn, E., Koda, V., . . . Bilder, R. M. (2002). Neurodevelopmental aspects of spatial navigation: a virtual reality fMRI study. *Neuroimage, 15*(2), 396-406.

Pober, B. R. (2010). Williams–Beuren Syndrome. *New England Journal of Medicine, 362*(3), 239-252. doi: 10.1056/NEJMra0903074

Podzebenko, K., Egan, G. F., & Watson, J. D. G. (2002). Widespread Dorsal Stream Activation during a Parametric Mental Rotation Task, Revealed with Functional Magnetic Resonance Imaging. *Neuroimage, 15*(3), 547-558. doi: 10.1006/nimg.2001.0999

Porter, M. A., Dobson-Stone, C., Kwok, J. B., Schofield, P. R., Beckett, W., & Tassabehji, M. (2012). A role for transcription factor GTF2IRD2 in executive function in Williams-Beuren syndrome. *PLoS One, 7*(10), e47457. doi: 10.1371/journal.pone.0047457

Presson, C. C., & Montello, D. R. (1988). Points of reference in spatial cognition: Stalking the elusive landmark*. *British Journal of Developmental Psychology, 6*(4), 378-381. doi: 10.1111/j.2044-835X.1988.tb01113.x

Preus, M. (1984). The Williams syndrome: objective definition and diagnosis. *Clin Genet, 25*(5), 422-428.

Purser, H. R., Farran, E. K., Courbois, Y., Lemahieu, A., Mellier, D., Sockeel, P., & Blades, M. (2012). Short-term memory, executive control, and children's route learning. *Journal of Experimental Child Psychology*. doi: 10.1016/j.jecp.2012.06.005

Purser, H. R., Farran, E. K., Courbois, Y., Lemahieu, A., Sockeel, P., Mellier, D., & Blades, M. (in press). The development of route learning in Down syndrome, Williams syndrome

and typical development: investigations with virtual environments. *Developmental Science*.

Quaiser-Pohl, C., Lehmann, W., & Eid, M. (2004). The relationship between spatial abilities and representations of large-scale space in children--a structural equation modeling analysis. *Personality and Individual Differences, 36*(1), 95-107. doi: 10.1016/S0191-8869(03)00071-0

Raven, J., Raven, J. C., & Court, J. H. (2003). *Manual for Raven's Progressive Matrices and Vocabulary Scales*. San Antonio, TX: Harcourt Assessment.

Regian, J. W., & Yadrick, R. M. (1994). Assessment of configurational knowledge of naturally- and artificially-acquired large-scale space. *Journal of Environmental Psychology, 14*(3), 211-223. doi: 10.1016/S0272-4944(94)80057-X

Reiss, A. L., Eckert, M. A., Rose, F. E., Karchemskiy, A., Kesler, S., Chang, M., . . . Galaburda, A. (2004). An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome. *J Neurosci, 24*(21), 5009-5015. doi: 10.1523/jneurosci.5272-03.2004

Richardson, A. E., Montello, D. R., & Hegarty, M. (1999). Spatial knowledge acquisition from maps and from navigation in real and virtual environments. *Memory and Cognition, 27*(4), 741-750.

Roberts, R. J., Jr., & Aman, C. J. (1993). Developmental differences in giving directions: spatial frames of reference and mental rotation. *Child Development, 64*(4), 1258-1270. doi: 10.1111/j.1467-8624.1993.tb04199.x

Rolls, E. T., & Kesner, R. P. (2006). A computational theory of hippocampal function, and empirical tests of the theory. *Progress in Neurobiology, 79*(1), 1-48. doi: 10.1016/j.pneurobio.2006.04.005

Rondan, C., Mancini, J., Livet, M.-O., & Deruelle, C. (2003). Perceptual and visuo constructive performance in children with Williams syndrome. *Cognition, Brain, Behavior, 7*, 149-157.

Rondi-Reig, L., Petit, G., Arelo, A., & Burguiere, E. (2005). *The starmaze: a new paradigm to characterize multiple spatial navigation strategies.* Paper presented at the 5th

International Conference on Methods and Techniques in Behavioural Research, Wageningen.

Rondi-Reig, L., Petit, G. H., Tobin, C., Tonegawa, S., Mariani, J., & Berthoz, A. (2006). Impaired sequential egocentric and allocentric memories in forebrain-specific–NMDA receptor knock-out mice during a new task dissociating strategies of navigation. *The journal of Neuroscience, 26*(15), 4071-4081.

Rose, F. D., Attree, E. A., Brooks, B. M., Parslow, D. M., Penn, P. R., & Ambihaipahan, N. (2000). Training in virtual environments: transfer to real world tasks and equivalence to real task training. *Ergonomics, 43*(4), 494-511. doi: 10.1080/001401300184378

Rossen, M., Bihrle, A., Klima, E. S., Bellugi, U., & Jones, W. (1996). Interaction between language and cognition: Evidence from Williams syndrome. In J. H. Beitchman, N. Cohen, M. Konstantareas, & R. Tannock (Eds.), *Language, Learning and Behavior*. New York: Cambridge University Press.

Roy, A. L. (2012). Biochemistry and biology of the inducible multifunctional transcription factor TFII-I: 10 years later. *Gene, 492*(1), 32-41. doi: 10.1016/j.gene.2011.10.030

Ruddle, R. A., Payne, S. J., & Jones, D. M. (1997). Navigating buildings in" desk-top" virtual environments: Experimental investigations using extended navigational experience. *Journal of Experimental Psychology: Applied, 3*(2), 143.

Ruddle, R. A., Volkova, E., Mohler, B., & Bülthoff, H. H. (2011). The effect of landmark and body-based sensory information on route knowledge. *Memory & Cognition, 39*(4), 686-699. doi: 10.3758/s13421-010-0054-z

Salatas, H., & Flavell, J. H. (1976). Perspective Taking: The Development of Two Components of Knowledge. *Child Development, 47*(1), 103-109.

Scerif, G., & Karmiloff-Smith, A. (2005). The dawn of cognitive genetics? Crucial developmental caveats. *Trends in Cognitive Sciences, 9*(3), 126-135. doi: 10.1016/j.tics.2005.01.008

Schinazi, V. R., & Epstein, R. A. (2010). Neural correlates of real-world route learning. *Neuroimage, 53*(2), 725-735. doi: 10.1016/j.neuroimage.2010.06.065

Schubert, C. (2009). The genomic basis of the Williams – Beuren syndrome. *Cellular and Molecular Life Sciences, 66*(7), 1178-1197. doi: 10.1007/s00018-008-8401-y

Scott, R., & Olson, M. (2007). LIM kinases: function, regulation and association with human disease. *Journal of Molecular Medicine, 85*(6), 555-568. doi: 10.1007/s00109-007-0165-6

Seubert, J., Humphreys, G. W., Muller, H. J., & Gramann, K. (2008). Straight after the turn: the role of the parietal lobes in egocentric space processing. *Neurocase, 14*(2), 204-219. doi: 10.1080/13554790802108398

Shelton, A. L., & Gabrieli, J. D. (2002). Neural correlates of encoding space from route and survey perspectives. *Journal of Neuroscience, 22*(7), 2711-2717.

Shelton, A. L., & Gabrieli, J. D. (2004). Neural correlates of individual differences in spatial learning strategies. *Neuropsychology, 18*(3), 442-449. doi: 10.1037/0894-4105.18.3.442

Shelton, A. L., & McNamara, T. P. (2001). Systems of Spatial Reference in Human Memory. *Cognitive Psychology, 43*(4), 274-310. doi: 10.1006/cogp.2001.0758

Shepard, R. N., & Cooper, L. A. (1982). *Mental Images and their Transformations*. Cambridge, MA: MIT Press.

Shepard, R. N., & Metzler, J. (1971). Mental Rotation of Three-Dimensional Objects. *Science, 171*(3972), 701-703. doi: 10.1126/science.171.3972.701

Siegel, A. W., Herman, J. F., Allen, G. L., & Kirasic, K. C. (1979). The Development of Cognitive Maps of Large- and Small-Scale Spaces. *Child Development, 50*(2), 582-585.

Siegel, A. W., & Schadler, M. (1977). The Development of Young Children's Spatial Representations of Their Classrooms. *Child Development, 48*(2), 388-394.

Siegel, A. W., & White, S. H. (1975). The development of spatial representations of large-scale environments. In H. W. Reese (Ed.), *Advances in Child Development and Behavior* (Vol. 10, pp. 531-549). New York: Academic Press.

Simons, D. J., & Wang, R. F. (1998). Perceiving real-world viewpoint changes. *Psychological Science, 9*, 315-320. doi: 10.1111/1467-9280.00062

Smith, A. D., Gilchrist, I. D., Hood, B., Tassabehji, M., & Karmiloff-Smith, A. (2009). Inefficient search of large-scale space in Williams syndrome: Further insights on the role of LIMK1 deletion in deficits of spatial cognition. *Perception, 38*(5), 694-701. doi: 10.1068/p6050

Spiers, H. J., Burgess, N., Hartley, T., Vargha-Khadem, F., & O'Keefe, J. (2001). Bilateral hippocampal pathology impairs topographical and episodic memory but not visual pattern matching. *Hippocampus, 11*(6), 715-725.

Spiers, H. J., & Maguire, E. A. (2007). A navigational guidance system in the human brain. *Hippocampus, 17*(8), 618-626. doi: 10.1002/hipo.20298

Stanton, D., Foreman, N., & Wilson, P. N. (1998). Uses of virtual reality in clinical training: developing the spatial skills of children with mobility impairments. *Studies in Health Technology & Informatics, 58*, 219-232.

Steck, S. D., & Mallot, H. A. (2000). The Role of Global and Local Landmarks in Virtual Environment Navigation. *Presence: Teleoperators and Virtual Environments, 9*(1), 69-83. doi: 10.1162/105474600566628

Steele, A., Scerif, G., Cornish, K., & Karmiloff-Smith, A. (2013). Learning to read in Williams syndrome and Down syndrome: syndrome-specific precursors and developmental trajectories. *Journal of Child Psychology and Psychiatry, 54*(7), 754-762. doi: 10.1111/jcpp.12070

Stinton, C., Farran, E. K., & Courbois, Y. (2008). Mental rotation in Williams syndrome: an impaired ability. *Developmental Neuropsychology, 33*(5), 565-583. doi: 10.1080/87565640802254323

Strømme, P., Bjømstad, P. G., & Ramstad, K. (2002). Prevalence Estimation of Williams Syndrome. *Journal of Child Neurology, 17*(4), 269-271. doi: 10.1177/088307380201700406

Sutton, J. E. (2006). The development of landmark and beacon use in young children: evidence from a touchscreen search task. *Developmental Science, 9*(1), 108-123. doi: 10.1111/j.1467-7687.2005.00467.x

Tassabehji, M. (2003). Williams–Beuren syndrome: a challenge for genotype–phenotype correlations. *Human Molecular Genetics, 12*(suppl 2), R229-R237. doi: 10.1093/hmg/ddg299

Tassabehji, M., Hammond, P., Karmiloff-Smith, A., Thompson, P., Thorgeirsson, S. S., Durkin, M. E., . . . Donnai, D. (2005). GTF2IRD1 in Craniofacial Development of Humans and Mice. *Science, 310*(5751), 1184-1187. doi: 10.1126/science.1116142

Tassabehji, M., Metcalfe, K., Karmiloff-Smith, A., Carette, M. J., Grant, J., Dennis, N., . . . Donnai, D. (1999). Williams Syndrome: Use of Chromosomal Microdeletions as a Tool to Dissect Cognitive and Physical Phenotypes. *American Journal of Human Genetics, 64*(1), 118-125. doi: 10.1086/302214

Taube, J. S. (1998). Head direction cells and the neurophysiological basis for a sense of direction. *Progress in Neurobiology, 55*(3), 225-256. doi: 10.1016/S0301-0082(98)00004-5

Taylor, H. A., Naylor, S. J., & Chechile, N. A. (1999). Goal-specific influences on the representation of spatial perspective. *Memory & cognition, 27*(2), 309-319.

Thomas, M. S. C., Grant, J., Barham, Z., Gsödl, M., Laing, E., Lakusta, L., . . . Karmiloff-Smith, A. (2001). Past tense formation in Williams syndrome. *Language and Cognitive Processes, 16*(2), 143 - 176.

Thomas, M. S. C., Purser, H. R., & Van Herwegen, J. (2012). Cognition: The developmental trajectory approach. In E. Farran & A. Karmiloff-Smith (Eds.), *Neurodevelopmental Disorders Across the Lifespan: A Neuroconstructivist Approach*. New York: Oxford University Press Inc.

Thorndyke, P. W., & Goldin, S. E. (1983). Spatial learning and reasoning skill. In H. L. Pick & L. P. Acredolo (Eds.), *Spatial orientation: Theory, research, and application* (pp. 195-217). New York: Plenum.

Thorndyke, P. W., & Hayes-Roth, B. (1982). Differences in spatial knowledge acquired from maps and navigation. *Cognitive Psychology, 14*(4), 560-589.

Tipney, H. J., Hinsley, T. A., Brass, A., Metcalfe, K., Donnai, D., & Tassabehji, M. (2004). Isolation and characterisation of GTF2IRD2, a novel fusion gene and member of the

TFII-I family of transcription factors, deleted in Williams-Beuren syndrome. *European Journal of Human Genetics, 12*(7), 551-560. doi: 10.1038/sj.ejhg.5201174

Tlauka, M., & Wilson, P. N. (1994). The effect of landmarks on route-learning in a computer-simulated environment. *Journal of Environmental Psychology, 14*(4), 305-313. doi: 10.1016/S0272-4944(05)80221-X

Tolman, E. C., Ritchie, B. F., & Kalish, D. (1946). Studies in spatial learning: II. Place learning versus route learning. *Journal of Experimental Psychology: General, 36*, 221-229.

Tversky, B., Bauer Morrison, J., Franklin, N., & Bryant, D. J. (1999). Three Spaces of Spatial Cognition. *The Professional Geographer, 51*(4), 516-524. doi: 10.1111/0033-0124.00189

Uttal, D. H., Sandstrom, L. B., & Newcombe, N. S. (2006). One Hidden Object, Two Spatial Codes: Young Children's Use of Relational and Vector Coding. *Journal of Cognition and Development, 7*(4), 503 - 525. doi: 10.1207/s15327647jcd0704_4

Valero, M. C., de Luis, O., Cruces, J., & Perez Jurado, L. A. (2000). Fine-scale comparative mapping of the human 7q11.23 region and the orthologous region on mouse chromosome 5G: the low-copy repeats that flank the Williams-Beuren syndrome deletion arose at breakpoint sites of an evolutionary inversion(s). *Genomics, 69*(1), 1-13. doi: 10.1006/geno.2000.6312

Van Herwegen, J., Farran, E., & Annaz, D. (2011). Item and error analysis on Raven's Coloured Progressive Matrices in Williams Syndrome. *Research in Developmental Disabilities, 32*(1), 93-99. doi: 10.1016/j.ridd.2010.09.005

Vandenberg, S. G., & Kuse, A. R. (1978). Mental rotations, a group test of three-dimensional spatial visualization. *Perceptual and Motor Skills, 47*(2), 599-604. doi: 10.2466/pms.1978.47.2.599

Vandeweyer, G., Van der Aa, N., Reyniers, E., & Kooy, R. F. (2012). The contribution of CLIP2 haploinsufficiency to the clinical manifestations of the Williams-Beuren syndrome. *American Journal of Human Genetics, 90*(6), 1071-1078. doi: 10.1016/j.ajhg.2012.04.020

Vann, S. D., Aggleton, J. P., & Maguire, E. A. (2009). What does the retrosplenial cortex do? *Nature Reviews Neuroscience, 10*(11), 792-802. doi: 10.1038/nrn2733

Vicari, S., Bellucci, S., & Carlesimo, G. A. (2000). Implicit and explicit memory: a functional dissociation in persons with Down syndrome. *Neuropsychologia, 38*(3), 240-251. doi: 10.1016/S0028-3932(99)00081-0

Vicari, S., Bellucci, S., & Carlesimo, G. A. (2001). Procedural learning deficit in children with Williams syndrome. *Neuropsychologia, 39*(7), 665-677. doi: 10.1016/S0028-3932(01)00012-4

Vicari, S., Bellucci, S., & Carlesimo, G. A. (2003). Visual and spatial working memory dissociation: evidence from Williams syndrome. *Developmental Medicine and Child Neurology, 45*(4), 269-273. doi: 10.1111/j.1469-8749.2003.tb00342.x

Vicari, S., Bellucci, S., & Carlesimo, G. A. (2006). Evidence from two genetic syndromes for the independence of spatial and visual working memory. *Developmental Medicine and Child Neurology, 48*(2), 126-131. doi: 10.1017/s0012162206000272

Vicari, S., Brizzolara, D., Carlesimo, G. A., Pezzini, G., & Volterra, V. (1996). Memory abilities in children with Williams syndrome. *Cortex, 32*(3), 503-514.

Voyer, D., Voyer, S., & Bryden, M. P. (1995). Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. *Psychological Bulletin, 117*(2), 250-270. doi: 10.1037/0033-2909.117.2.250

Waller, D., & Lippa, Y. (2007). Landmarks as beacons and associative cues: their role in route learning. *Memory and Cognition, 35*(5), 910-924.

Waller, D., Loomis, J. M., & Steck, S. D. (2003). Inertial cues do not enhance knowledge of environmental layout. *Psychonomic Bulletin & Review, 10*(4), 987-993.

Waller, D., Montello, D. R., Richardson, A. E., & Hegarty, M. (2002). Orientation specificity and spatial updating of memories for layouts. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 28*(6), 1051-1063.

Wallet, G., Sauzéon, H., Rodrigues, J., & NKaoua, B. (2009). Transfer of spatial knowledge from a virtual environment to reality: Impact of route complexity and subject's strategy on the exploration mode. *Journal of Virtual Reality and Broadcasting 6*(4), 1860-2037.

Walsh, D. A., Krauss, I. K., & Regnier, V. A. (1981). Spatial ability, environmental knowledge, and environmental use. In L. S. Liben, A. Patterson, & N. Newcombe (Eds.), *Spatial Representation and Behavior across the Life Span*. New York: Academic Press.

Wang, L., Mou, W., & Sun, X. (2013). Development of Landmark Knowledge at Decision Points. *Spatial Cognition & Computation, 14*(1), 1-17. doi: 10.1080/13875868.2013.784768

Wang, R. F., & Spelke, E. (2002). Human spatial representation: insights from animals. *Trends in Cognitive Sciences, 6*(9), 376.

Wechsler, D. (1949). *The Wechsler Intelligence Scale for Children*. New York: The Psychological Corporation.

Wechsler, D. (1989). *Wechsler Preschool and Primary Scale of Intelligence- Revised*. San Antonio, TX: The Psychological Corporation.

Wen, W., Ishikawa, T., & Sato, T. (2013). Individual Differences in the Encoding Processes of Egocentric and Allocentric Survey Knowledge. *Cognitive Science, 37*(1), 176-192. doi: 10.1111/cogs.12005

Weniger, G., Ruhleder, M., Wolf, S., Lange, C., & Irle, E. (2009). Egocentric memory impaired and allocentric memory intact as assessed by virtual reality in subjects with unilateral parietal cortex lesions. *Neuropsychologia, 47*(1), 59-69. doi: 10.1016/j.neuropsychologia.2008.08.018

Weniger, G., Siemerkus, J., Schmidt-Samoa, C., Mehlitz, M., Baudewig, J., Dechent, P., & Irle, E. (2010). The human parahippocampal cortex subserves egocentric spatial learning during navigation in a virtual maze. *Neurobiology of Learning and Memory, 93*(1), 46-55. doi: 10.1016/j.nlm.2009.08.003

Wilson, P. N., Foreman, N., & Tlauka, M. (1996). Transfer of spatial information from a virtual to a real environment in physically disabled children. *Disability and Rehabilitation, 18*(12), 633-637. doi: 10.3109/09638289609166328

Wolbers, T., & Buchel, C. (2005). Dissociable retrosplenial and hippocampal contributions to successful formation of survey representations. *Journal of Neuroscience, 25*(13), 3333-3340. doi: 10.1523/jneurosci.4705-04.2005

Wolbers, T., & Hegarty, M. (2010). What determines our navigational abilities? *Trends in Cognitive Sciences, 14*(3), 138-146. doi: 10.1016/j.tics.2010.01.001

Wolbers, T., Weiller, C., & Büchel, C. (2004). Neural foundations of emerging route knowledge in complex spatial environments. *Cognitive Brain Research, 21*(3), 401-411. doi: 10.1016/j.cogbrainres.2004.06.013

Wraga, M., Creem, S. H., & Proffitt, D. R. (1999). The influence of spatial reference frames on imagined object- and viewer rotations. *Acta Psychologica, 102*(2-3), 247-264. doi: 10.1016/S0001-6918(98)00057-2

Wraga, M., Creem, S. H., & Proffitt, D. R. (2000). Updating scenes after obejct- and viewer rotations. *Journal of Experimental Psychology: Learning Memory and Cognition, 102*, 247-264. doi: 10.1037/0278-7393.26.1.151

Wraga, M., Shephard, J. M., Church, J. A., Inati, S., & Kosslyn, S. M. (2005). Imagined rotations of self versus objects: an fMRI study. *Neuropsychologia, 43*(9), 1351-1361. doi: 10.1016/j.neuropsychologia.2004.11.028

Xistouri, X., & Pitta-Pantazi, D. (2006). *Spatial rotation and perspective taking abilities in relation to performance in reflective symmetry tasks.* Paper presented at the 30th Proceedings of the Conference of the International Group for the Psychology of Mathematics Education. Volume 5, Prague, Czech Republic.

Yagihashi, T., Torii, C., Takahashi, R., Omori, M., Kosaki, R., Yoshihashi, H., . . . Kosaki, K. (2014). Clinical Utility of an Array Comparative Genomic Hybridization Analysis for Williams Syndrome. *Congenital Anomalies*, n/a-n/a. doi: 10.1111/cga.12065

Young, E. J., Lipina, T., Tam, E., Mandel, A., Clapcote, S. J., Bechard, A. R., . . . Osborne, L. R. (2008). Reduced fear and aggression and altered serotonin metabolism in Gtf2ird1-targeted mice. *Genes, Brain, and Behavior, 7*(2), 224-234. doi: 10.1111/j.1601-183X.2007.00343.x

Zacks, J. M. (2008). Neuroimaging Studies of Mental Rotation: A Meta-analysis and Review. *Journal of Cognitive Neuroscience, 20*(1), 1-19. doi: 10.1162/jocn.2008.20013

Zacks, J. M., & Michelon, P. (2005). Transformations of Visuospatial Images. *Behavioral and Cognitive Neuroscience Reviews, 4*(2), 96-118. doi: 10.1177/1534582305281085

Zacks, J. M., Mires, J., Tversky, B., & Hazeltine, E. (2000). Mental spatial transformations of objects and perspective. *Spatial Cognition and Computation, 2*(4), 315-332. doi: 10.1023/a:1015584100204

Zacks, J. M., Ollinger, J. M., Sheridan, M. A., & Tversky, B. (2002). A Parametric Study of Mental Spatial Transformations of Bodies. *Neuroimage, 16*(4), 857-872. doi: 10.1006/nimg.2002.1129

Zacks, J. M., Rypma, B., Gabrieli, J. D. E., Tversky, B., & Glover, G. H. (1999). Imagined transformations of bodies: an fMRI investigation. *Neuropsychologia, 37*(9), 1029-1040. doi: 10.1016/S0028-3932(99)00012-3

Zacks, J. M., Vettel, J. M., & Michelon, P. (2003). Imagined viewer and object rotations dissociated with event-related FMRI. *Journal of Cognitive Neuroscience, 15*(7), 1002-1018. doi: 10.1162/089892903770007399